The Journal of Thoracic Surgery

VOL. 23 JANUARY, 1952 NO. 1

Original Communications

CONSTRICTIVE PERICARDITIS AND CONSTRICTIVE PLEURITIS TREATED BY PERICARDIECTOMY AND PULMONARY DECORTICATION

REPORT OF A CASE

RICHARD H. OVERHOLT, M.D.,* C. SIDNEY BURWELL, M.D.** (BY INVITATION), JOHN W. WOODBURY, M.D.*** (BY INVITATION), AND JAMES H. WALKER, M.D.§ (BY INVITATION)

BOSTON, MASS.

CONSTRICTION of the pericardium and pleura represents an unfortunate paradox in which the process of healing creates a disability greater than the original disorder. Since the function of both heart and lung is dependent upon expansion and contraction, disability is proportionate to the area and the degree of inelasticity of the constricting scar.

Constrictive pleuritis is the more common. Although it limits ventilation and, therefore, may be disabling, it is in itself rarely fatal. Constrictive pericarditis is less frequent; if severe, it is disabling and may progress to a fatal conclusion. Should these two constrictions occur simultaneously, the chances for a successful pericardiectomy will be greater with recognition and remedy of the pleuritis.

The only recorded recognition of combined constrictive disability of heart and lung was published by Burwell and Ayer[1] in 1941. The disease was of tuberculous etiology. A pericardiectomy relieved the associated circulatory effects, but death resulted from extreme ventilatory insufficiency produced by the pulmonary immobility.

There are four reasons for our presentation of another case of this combined constrictive disability: (1) unusual etiology, (2) preoperative recognition, (3)

From the Department of Surgery, Tufts College Medical School.

Read at the Thirty-first Annual Meeting of The American Association for Thoracic Surgery, Atlantic City, N. J., April 16-18, 1951.

*Thoracic Surgeon, New England Deaconess and New England Center Hospitals.

**Research Professor of Clinical Medicine, Harvard Medical School. Physician to the Peter Bent Brigham Hospital.

***Public Health Service Research Fellow of the National Heart Institute, Peter Bent Brigham Hospital.

§Thoracic Surgeon, New England Deaconess Hospital.

LIBRARY
BOSTON UNIVERSITY
SCHOOL OF MEDICINE

simultaneous and successful treatment, and (4) a new operative approach for pericardiectomy.

CASE REPORT

T. J. F., a 50-year-old white unemployed painter was admitted to the New England Deaconess Hospital on July 5, 1950, with complaints of cough, dyspnea, and progressive edema. In February, 1945, this patient received a nonpenetrating injury to the chest when he was crushed against a concrete pillbox by a truck. He was hospitalized for many months with bilateral numerous rib fractures and hemothoraces. He was treated with rib traction, body cast, and bilateral closed catheter drainage. Since the injury, he had had gradually increasing exertional dyspnea, orthopnea, and paroxysmal nocturnal dyspnea. Repeated respiratory infections, characterized by severe dyspnea and cough, had necessitated hospitalization for oxygen, bronchodilator, and antibiotic therapy. At least one of these episodes was accompanied by substernal pain. Progressive edema and ascites, unsuccessfully treated with digitalis and diuretics, had been present for six months prior to admission.

Physical Examination.—The patient was a moderately dyspneic and orthopneic man with visibly distended neck veins and engorged retinal veins. The chest was held in an inspiratory position, and the anteroposterior diameter was definitely increased. The left side moved considerably more than the right, and the right lower chest almost not at all. Dullness and decreased breath sounds were present at the right base, and there were fine râles at both bases. The heart was not grossly enlarged; its rhythm was regular; and its sounds were distant and unaccompanied by murmurs. There was a marked *pulsus paradoxicus* with a fall in systolic blood pressure of 15 mm. Hg on inspiration. There was extensive edema, most marked in the lower half of the body, but present also in the arms. Liver dullness extended two fingerbreadths below the right costal margin.

Laboratory Findings.—Hemoglobin was 15 mg. per cent, with a hematocrit of 47 per cent. Electrocardiogram showed low to inverted T waves and low EMF of QRS in all leads. Chest film showed numerous old rib fractures with markedly thickened pleura over all surfaces of the lungs and obliteration of the right costophrenic angle (Fig. 1). At fluoroscopy, the right diaphragm moved only 1 cm., the left, 4 cm. The heart was not enlarged, but amplitude of the heartbeat was much reduced on all borders. No pericardial calcification was seen. Venous pressure in both antecubital and femoral veins was 350 mm. of saline.

Course.—The preoperative pulmonary function studies were done on July 15, 1950, and cardiac catheterization on July 17, 1950. Decortication of the left lung and the heart was done under local anesthesia with the patient in the prone position on July 26, 1950. The pleural space was found to be completely obliterated, and the scar measured 2 to 3 mm. in thickness. The pulmonary decortication was accomplished with ease, and complete expansion of the lung was observed. There was no evidence by inspection or palpation of parenchymal pulmonary disease. The cardiac pulsations were markedly diminished by a thick, fibrotic layer of tissues, largely replacing the pericardium and densely adherent to the myocardium. This thickened pericardium measured 4 to 5 mm. in thickness. No calcification was observed. The constricting pericardial membrane was removed from the entire surface of the left ventricle and from a portion of the right ventricle and of the left auricle. Following this the cardiac pulsations appeared normal. During the actual removal of the cicatrix, cardiac arrhythmias developed on several occasions, but returned to normal following rest from the manipulation. A short episode of cardiac standstill responded quickly and favorably to cardiac massage. The phrenic nerve was carefully dissected from the cicatrix, and at completion of the surgical procedure the diaphragmatic motions on the left were noted to be normal. The venous pressure was 180 mm. of saline three weeks postoperatively, and 140 mm. of saline five months later. Decortication of the right lung was performed on Dec. 11, 1950. The pleural space was completely obliterated, and the thickened scarred membrane was more dense and adherent than that encountered in the left hemithorax. This membrane measured 2 to 4 mm. in thickness. Following decortication, there was pulmonary expansion. No gross evidence of pulmonary

parenchymal disease was observed. Inspection of the heart and pericardium on the right side revealed pulsations to be normal, and there was no evidence of any constrictive phenomenon. The postoperative course was uncomplicated. The pulmonary function studies were repeated on March 17, 1951, and cardiac catheterization on March 19, 1951.

Etiology.—The cause of the pericardial and pleural cicatrix in this case is of particular interest. There was no microscopic evidence of tuberculosis in any of the specimens, and the pleural membrane had none of the gross characteristics of the peel resulting from empyema, tuberculous or otherwise. It is known that the patient had bilateral hemothoraces following his crushing injury; however, it is highly unlikely these ever became infected since open drainage was never necessary, and since at pulmonary decortication no empyema

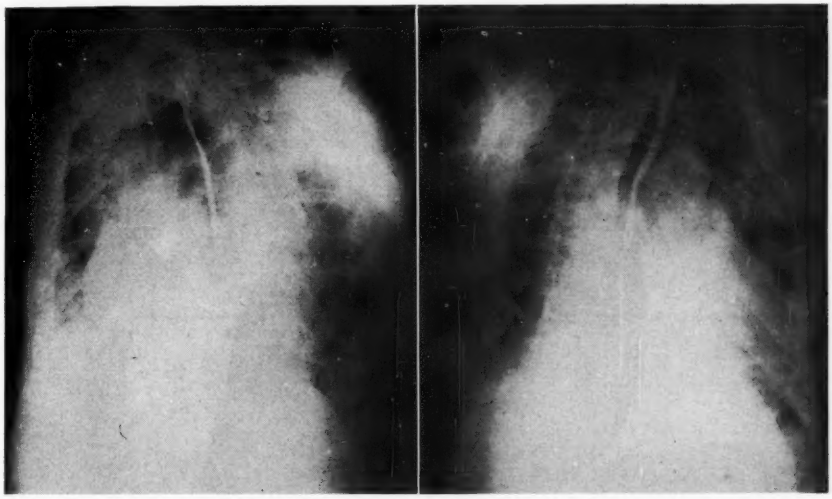


Fig. 1.—Preoperative oblique roentgenogram. This demonstrates the bilaterally thickened pleural membrane.

pocket was found on either side. During his illness, there was no history suggestive of pericardial effusion or purulent pericarditis. We believe that this combined constrictive disability was the late result of a sterile hemothorax and hemopericardium. We have been unable to find a reported, well-substantiated case of constrictive pericarditis resulting from injury uncomplicated by infection. Warburg[2] has included in his monograph on nonpenetrating injuries of the heart a case of chest injury followed by a typical Pick's syndrome with pericardial calcification demonstrated by roentgenogram. No post-mortem examination was reported, however, and incidental tuberculosis in his patient cannot be excluded. A case reported by White and Glandy[3] had proved tuberculous constrictive pericarditis following a bloody pericardial effusion due to injury.

Cardiac Catheterization.—This patient was subjected to cardiac catheterization preoperatively and eight months after his pericardiectomy. Before presenting the actual pressure values obtained in our case, it may be worth while to

review the normal pressure-flow relationships in both systemic and pulmonary circuits and the various concepts of pressure alteration produced by constrictive pericarditis. The normal values for pressures within the heart and great vessels are presented in Fig. 2. In Fig. 3 are illustrated the possible sites at which obstruction to the circulation might be caused by constrictive pericarditis as postulated by various authors.[4-11] For purposes of illustration, hypothetical pressures which would have to be obtained with each site of obstruction are also noted. In our experience, the pressure relationships indicated in the three hypothetical cases have never been encountered.

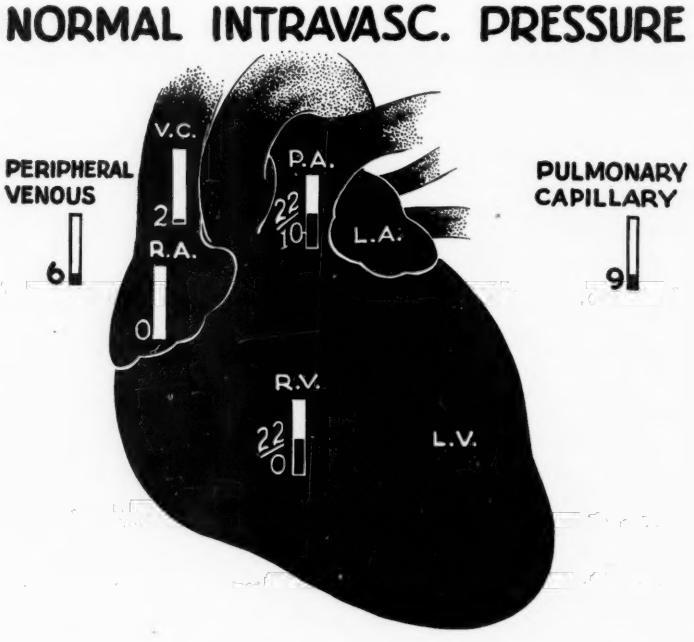


Fig. 2.

The normal values and the pre- and postoperative values of this patient are listed in Table I. It is to be noted that the "pulmonary capillary" pressure, pulmonary arterial diastolic pressure and right ventricular diastolic pressure are almost identical and markedly elevated preoperatively in our patient. These pressure changes are characteristic of constriction of the left ventricle.[11] The only recorded catheterization data in constrictive pericarditis have indicated that constriction of the left ventricle was present in every case (9 and 11); therefore, unless catheterization data clearly indicate in any individual case that marked constriction is present at any other site, it is the surgeon's responsibility to remove adequately the constricting scar over the left ventricle. Postoperative catheterization data in this patient show an increase in cardiac output (expressed as liters per minute per 100 c.c. of oxygen consumption) and in

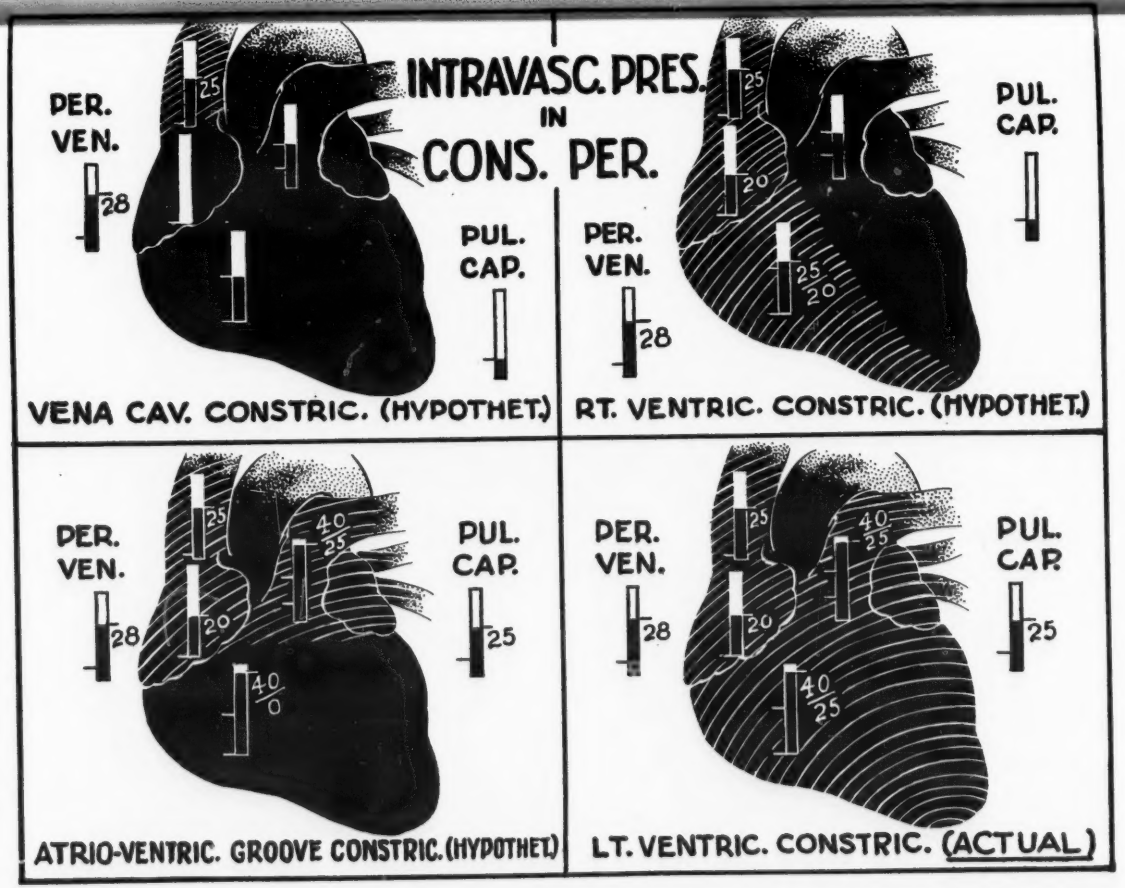


Fig. 3.—Diagram indicating intravascular pressures in constrictive pericarditis. The area of the curved white line represents elevated intravascular pressures due to constrictive pericarditis.

stroke index as well as a return of all pressures to near the normal values. The residual elevation of "pulmonary capillary" pressure may be attributable to left ventricular failure due to the myocardial atrophy seen routinely after pericardiectomy[12] or due to fibrosis of the myocardium.

TABLE I. CARDIAC CATHETERIZATION DATA

T. J. F. MALE, AGE 50				CONSTRICTIVE PERICARDITIS
		NORMAL RANGE	PREOPERATIVE JULY 17, 1950	8 MONTHS POSTOPERATIVE MARCH 19, 1951
Height (cm.)			165.5	165.5
Weight (Kg.)			71.6	63.6
Body surface (area M^2)			1.77	1.71
Intravascular pressures mm. Hg				
Peripheral arterial	(S/D)	120/80	134/82	155/81
Peripheral arterial	(mean)	100	95	118
"Pulmonary capillary"	(mean)	9	27	18
Pulmonary artery	(S/D)	22/10	45/29	34/12
Pulmonary artery	(mean)	12	34	22
Right ventricular	(S/D)	22/5/0	46/25/15	33/12/3
Right atrial	(mean)	0	22	7
Vena caval	(mean)	2	25	8
Peripheral venous	(mean)	6	27	8
Cardiac output				
Arterial oxygen content		(Vol. per cent)	19.25	19.45
Venous oxygen content		(Vol. per cent)	14.45	15.38
Arterial oxygen saturation		(per cent)	96	98
A-V difference		(c.c./L.)	48	41
Oxygen consumption		(c.c./min.)	222	319
Oxygen consumption		(c.c./min./M^2)	125	187
Ventilation		(L./min.)	7.8	12.0
Cardiac output		(L./min.)	4.6	8.0
Cardiac output		(L./min./100 c.c. O^2)	2.1	2.5
Cardiac index		(L./min./M^2)	2.6	4.7
Pulse rate		(beats/min.)	82	80
Stroke volume		(c.c./beat)	56	100
Stroke index		(c.c./beat/M^2)	32	58

TABLE II. VENTILATORY FUNCTION STUDIES

T. J. F. MALE, AGE 50			CONSTRICTIVE PLEURITIS AND PERICARDITIS	
		PREOPERATIVE JULY 15, 1950	POST LEFT DECORTICATION & PERICARDECTOMY DEC. 5, 1950	POST RIGHT DECORTICATION MARCH 17, 1951
Respiratory rate/min.		16	13	20
Tidal Air at Rest	(L.)	0.457	0.682	0.488
Resting Minute Volume	(L./min.)	7.30	8.52	10.05
Expiratory Capacity	(L.)	0.478	0.870	0.880
Inspiratory Capacity	(L.)	0.870	1.160	0.946
		1.190*	1.960	1.805
Vital Capacity	(L.)		1.940*	1.715*
			72.5	74.2
Maximum Breathing Capacity	(L./min.)	32.6*	53.0*	55.0*
			88.3	86.6
Resting Ventilatory Reserve	(per cent)	77.6*	84.0*	82.0*
Capacity Ratio $\left(\frac{MBC}{VC}\right)$			37.0	41.0
		27.4*	27.4*	32.0*

*Values obtained with valves and soda lime canister in ventilometer offering significant resistance.

Ventilatory Function Study.—Pulmonary decortication is now a standard procedure for incarcerated lung in chronic hemothorax, nonexpandable pneumothorax, and chronic empyema.[13, 14] Respiratory function studies in patients subjected to pulmonary decortication have been reported by several authors.[15-18] This experience indicates that excellent restoration of ventilation and gas exchange can be expected after decortication when the underlying lung parenchyma is not extensively diseased and when the incarceration has not been of excessive duration. Little benefit has been derived from decortication in most cases of mixed tuberculous empyema and in some of these decortication has made even worse the ventilation-perfusion relationship in a diseased lung by increasing its ventilation without increasing its oxygen uptake.[17, 18]

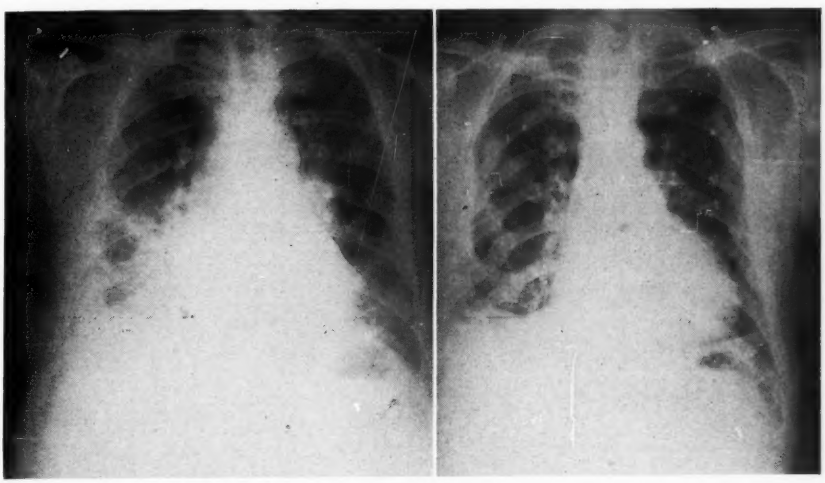


Fig. 4.—Preoperative posteroanterior roentgenograms of the chest (left). The numerous rib fractures and bony bridges are noted. The same projection postoperatively (right). Note the altered cardiac silhouette following the release from the pericardial constriction.

Most reported cases of hemothorax have been operated upon early in the course when loculated pockets of serum still remain and the organized peel has not yet become dense cicatrix.[19] In our case both lungs were encased in a tight, nonelastic membrane which visibly restricted expansion of the lungs at operation. Ventilatory function studies performed before the pericardiectomy and left pulmonary decortication, again just before the right pulmonary decortication, and a third time three months after the second operation, are presented in Table II. Had bronchospirometry been performed, it would be less difficult to distinguish the effect of pulmonary decortication from the relief of pulmonary congestion by the pericardiectomy. The marked improvement in vital capacity and maximum breathing capacity after the first operation is obvious. This patient had so much injury to ribs and intercostal muscles that his rib cage itself is the limiting factor in ventilation. This explains the failure to observe further improvement after the right pulmonary decortication. Chest films clearly show

numerous rib fragments in such malposition that considerable bony bridging has occurred between the ribs, accounting for much of the thoracic immobility (Figs. 4 and 5).

Operative Approach.—The pericardiectomy and left pulmonary decortication in this case were performed through a posterolateral transpleural approach with the patient in the prone position (Fig. 6). This approach for pericardiectomy is preferred by us, rather than the usual anterior and lateral thoracotomies, for the following reasons:

1. *Anatomic:* The major portion of the left ventricle is posterior to the left phrenic nerve. With the posterior approach, all surfaces of the left ventricle—anterior, lateral and posterior—are more accessible for surgery than with the anterior approaches. In addition, fair exposure of the right ventricle and left auricle is also obtained. Since the course of the phrenic nerve is easily seen, it is less likely to be injured.

Fig. 5.—Postoperative oblique roentgenogram. There is no evidence of thickened pleural membrane.

2. *Physiologic:* In the lateral position, controlled positive pressure anesthesia is required to maintain adequate ventilation. The impairment of venous return, decrease in cardiac output, and lowering of the blood pressure produced by positive pressure anesthesia aggravate these same circulatory effects of constrictive pericarditis. In addition, Beecher[20] has emphasized the presence of increased amounts of respiratory acidosis in the lateral position which is not present when supine or prone is used. For these physiologic reasons, the lateral approach should not be used.

3. *Technical:* A wide exposure of operative field is obtained with the posterior approach, and the depth is about one-half that of the anterior or lateral approaches. This makes for greater ease and safety during the tedious dissection of the adherent pericardium. With the anterior or lateral position, when there is an operative accident, the hemothorax acts as a basin to collect the blood which quickly hides the defect. With the prone position, this basin is not present and immediate attention can be focused on the repair of the defect.

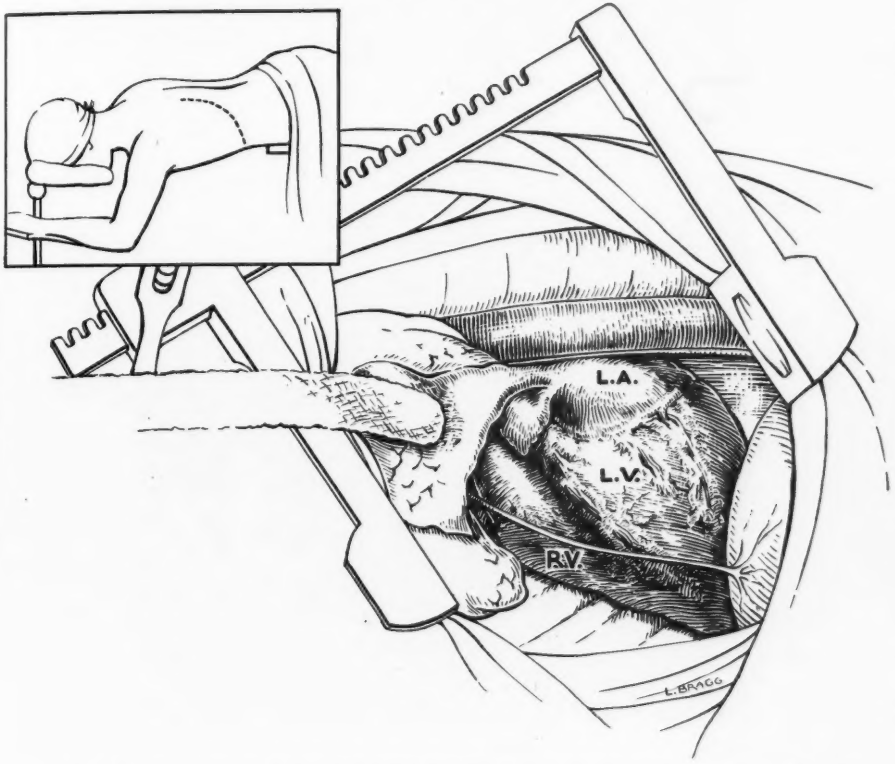


Fig. 6.—An anatomic drawing showing the excellent exposure for pericardiectomy with the patient in the prone position. The pericardium has been removed. The major portion of the left ventricle and a part of the right ventricle are posterior to the phrenic nerve. (*LA*, left auricle; *LV*, left ventricle; *RV*, right ventricle.)

Extent of Pericardiectomy.—In our experience, decortication of the left ventricle is necessary to insure maximum circulatory rehabilitation in constrictive pericarditis. We, therefore, practice and recommend excising the pericardium from the anterior, lateral, and *posterior* surfaces of the ventricles. The apex should be freed because it constitutes a portion of both ventricles. We have found no sound physiologic evidence to prove that the auriculo-ven-

tricular groove should be liberated. As a general rule, no attempt need be made to free the auricles, vena cava, pulmonary artery, or pulmonary veins unless this should be indicated by catheterization studies.

Fig. 7.—Postoperative photograph of the patient. Note the complete resolution of the edema.

SUMMARY

1. A patient with combined constrictive pericarditis and constrictive pleuritis successfully treated by pericardiectomy and bilateral pulmonary decortication is presented. As far as can be determined, this dual constrictive disability was the result of a crushing injury to the chest with uninfected bilateral hemothorax and hemopericardium.

2. Preoperatively, cardiac catheterization clearly demonstrated impaired function of the left ventricle. Pericardiectomy was specifically directed at

total decortication of the left ventricle. Postoperative catheterization data justified this technique by showing excellent return of pulmonary vascular pressures to nearly normal.

3. A new posterior operative approach for pericardiectomy which allows excellent exposure for decortication of the posterior and lateral surfaces of the heart is described. This approach was especially suited for the combined resection of constricting membranes from both the heart and left lung in this patient.

The complete study and treatment of this patient was made possible through the close cooperation of the Boston Regional Office of the Veterans Administration.

REFERENCES

1. Burwell, C. S., and Ayer, G. D.: Constrictive Pleuritis and Pericarditis, Am. Heart J. **22**: 267, 1941.
2. Warburg, E.: Subacute and Chronic Pericardial and Myocardial Lesions Due to Non-penetrating Traumatic Injuries, Copenhagen and London, 1938.
3. White, P. D., and Glendy, R. E.: Trauma and Heart Disease. (Trauma and Disease—Brahdy, Leopold and Kahn, Samuel) ed. 2, Philadelphia, 1941, Lea & Febiger, pp. 26-91.
4. Schmieden, V.: The Technique of Cardiolysis, Surg., Gynec., & Obst. **43**: 89, 1926.
5. Steart, H. J., and Heuer, G. J.: Chronic Constrictive Pericarditis: Dynamics of the Circulation and Result of Surgical Treatment, Arch. Int. Med. **63**: 504, 1939.
6. Blalock, A., and Burwell, C. S.: Chronic Pericardial Disease: Report of Twenty-eight Cases of Constrictive Pericarditis, Surg., Gynec., & Obst. **73**: 433, 1941.
7. Harrington, S. W.: Chronic Constrictive Pericarditis: Partial Pericardiectomy and Epicardiolysis in Twenty-four Cases, Ann. Surg. **120**: 468, 1944.
8. Churchill, E. D.: Pericardial Resection in Chronic Constrictive Pericarditis, Ann. Surg. **104**: 516, 1936.
9. White, P. D., Alexander, F., Churchill, E. D., and Sweet, R. H.: Chronic Constrictive Pericarditis Over the Left Heart Chambers and its Surgical Relief, Am. J. M. Sc. **216**: 378, 1948.
10. Holman, E., and Willett, F.: The Surgical Correction of Constrictive Pericarditis, Surg., Gynec., & Obst. **89**: 129, 1949.
11. Sawyer, C. G., Burwell, C. S., Dexter, L., Harkin, D., Eppinger, E. C., Haynes, F. W., Goodale, W. T., and Gorlin, R.: Chronic Constrictive Pericarditis: Further Consideration of the Pathological Physiology of the Disease, to be published.
12. Roberts, J. T., and Beck, C. S.: The Effect of Chronic Cardiac Compression on the Size of the Heart Muscle Fibers, Am. Heart J. **22**: 314, 1941.
13. Tuttle, W. M., Langston, H. T., and Crowley, R. T.: The Treatment of Organizing Hemothorax by Pulmonary Decortication, J. THORACIC SURG. **16**: 117, 1947.
14. Samson, Paul C., and Burford, T. H.: Total Pulmonary Decortication: Its Evolution and Present Concepts of Indications and Operative Technique, J. THORACIC SURG. **16**: 127, 1947.
15. Gordon, J., and Welles, E. S.: Decortication in Pulmonary Tuberculosis Including Studies of Respiratory Physiology, J. THORACIC SURG. **18**: 337, 1949.
16. Wright, G. W., Yee, L. B., Filley, G. F., and Stranahan, A.: Physiologic Observations Concerning Decortication of the Lung, J. THORACIC SURG. **18**: 372, 1949.
17. Carroll, D., McClement, J., Himmelstein, A., and Cournand, A.: Pulmonary Function Following Decortication of the Lung, Am. Rev. Tuberc. **63**: 231, 1951.
18. Gaensler, E. A.: Personal communication.
19. Langston, H. T., and Tuttle, W. M.: The Pathology of Chronic Traumatic Hemothorax. J. THORACIC SURG. **16**: 99, 1947.
20. Beecher, H. K., and Murphy, A. J.: Acidosis During Thoracic Surgery, J. THORACIC SURG. **19**: 50, 1950.

DISCUSSION

DR. CONRAD R. LAM, Detroit.—I should like to congratulate Dr. Overholt and his associates for the results they obtained in this case. However, I would like to state that I think they should not generalize too much with regard to the approach in a typical case of constrictive pericarditis. I should like to bear testimony for the good results

obtained by Dr. Holman's approach by median sternotomy. One can decorticate down to the phrenic nerve on each side quite easily, and the results in our hands in a small series of cases have been uniformly good.

DR. J. F. HIGGINSON, Portland, Ore.—I have had occasion to use three approaches to this problem, the circular pectoral flap approach, the left anterolateral approach which has also been described by the Boston group, and the sternal splitting approach. In contradistinction to the remarks made about how far one can reach posteriorly, it is possible by means of the sternal splitting approach to reach the back of the heart quite adequately. I think of all three approaches I have tried (I have not used this prone position) the sternal splitting approach is by far the best.

DR. EMILE HOLMAN, San Francisco.—I think this is an unusual course of events that produced this left ventricular compression, and is not comparable with the usual case of cardiac compression that we meet. I should like to state what we have found experimentally. We have had no difficulty whatsoever in producing all the symptoms of cardiac compression by constricting the right heart alone. We have four dogs for varying periods of time up to a year. Since constricting the left heart alone, we have had no symptoms whatsoever of the usual cardiac compression. I think we can prove this eventually.

DR. OVERHOLT (closing).—It was Professor Schmieden, as early as 1926, who pointed out very clearly that it was necessary to free completely the left ventricle. Since that time, there has been a great deal of argument as to whether or not the other portions of the heart should be freed or liberated. In reading over the discussion of Dr. Holman's paper which was given two years ago at the New Orleans meeting, it was apparent that the majority of discussers favored a complete exposure of the anterior surface of the heart in order to make sure that the decortication was extended to include the vena cava. In this connection, however, the observations of Dexter and Burwell are interesting. Dr. Dexter catheterized for Dr. Sweet in 1947 a patient who had been operated upon on two occasions in which the anterior approach had been used. The patient was not adequately relieved. It was demonstrated that this patient still had left ventricular constriction. Since that time, Dr. Dexter has had an opportunity to catheterize other patients in which the difficulty was found to be entirely left ventricular constriction. Dr. Sweet asked me this morning, since he could not be here, if I would not report that in his experience he has never seen any evidence that there was obstruction on the right border of the heart in cases observed at the Massachusetts General Hospital.

This particular patient that Dr. Walker has presented was unique in that the co-existing bilateral constricting pleuritis required liberation of both lung and heart from their constricting membranes. It forced us to open widely both pleural cavities and to plan the first procedure in such a way that there be complete access to the entire lung and left ventricle. The second operation afforded an opportunity to verify Dr. Burwell's and Dr. Dexter's prediction that we would not find obstruction on the right side. After decortication of the right lung, we found that there was no superior or inferior vena caval obstruction and no further decortication of the heart was required. Interestingly enough, this was our most seriously crippled patient and yet, by the posterior approach with attention to the left ventricle, our best result was obtained. Recently, we have found it necessary to reoperate upon a patient because there was an overlooked associated constrictive pleuritis, and the left ventricle had been inadequately liberated through an anterior approach. These experiences have caused us to pay more attention to the possibility of co-existing constriction of the lung as well as the heart, particularly in tuberculous subjects. It has also convinced us that the posterolateral approach in the face-down position provides a most satisfactory approach to both the left lung and posterior lateral aspect of the heart.

DR. WOODBURY (closing).—The technique of cardiac catheterization applied to patients with constrictive pericarditis has elucidated the pathologic physiology of this disease in a definitive manner which deductions from anatomy, observations at operation, and experiments in dogs have not done.

Our laboratory has catheterized eight patients who subsequently at operation were proved to have constrictive pericarditis. In none of these patients was there an increased pressure gradient between peripheral vein and right atrium. This rules out significant vena caval constriction as the cause of the elevated peripheral venous pressure. In none of these patients was there an increased gradient between right atrial pressure and right ventricular end-diastolic pressure. This rules out significant atrio-ventricular groove constriction as the cause of the elevated peripheral venous and right atrial pressures. Dr. Hansen of Copenhagen has catheterized ten patients with constrictive pericarditis, and he reports in a personal communication that he has never found pressure gradients in the great vessels indicating localized constriction at any point.

In view of this evidence against isolated stenosis, the alternative explanation for the elevated venous pressures and the diminished cardiac output in constrictive pericarditis must be embarrassment of ventricular function. That this interference is not confined to the right ventricle alone is indicated by the observation that pulmonary capillary and pulmonary arterial pressures were elevated in every one of these eighteen cases. In the eight cases catheterized in our laboratory pulmonary capillary pressures ranged from 16 to 28 mm. of mercury, two to three times the normal, and in six of the eight it was higher than right atrial pressure. Such high left ventricular filling pressures indicate that the reduced stroke volume found in every case must be due either to left ventricular failure or to limitation of left ventricular filling by a constricting pericardium.

On the basis of this evidence we are convinced that the left ventricle should be completely liberated whenever pericardiectomy is performed for constrictive pericarditis.

THE DIRECT INTRACARDIAC RELIEF OF PULMONARY STENOSIS IN THE TETRALOGY OF FALLOT

ROBERT P. GLOVER, M.D., CHARLES P. BAILEY, M.D., THOMAS J. E. O'NEILL, M.D., DANIEL F. DOWNING, M.D. (BY INVITATION), AND C. ROBERT E. WELLS, M.D. (BY INVITATION)
PHILADELPHIA, PA.

ALTHOUGH a considerable volume of anatomic, pathologic, physiologic, and clinical data regarding the nature of cyanotic heart diseases existed prior to 1945, these conditions aroused little interest or enthusiasm when considered therapeutically. The variety of malformations described were of so complicated a nature, the victims so pitifully afflicted, and the underlying physiologic changes so little understood or appreciated that the entire subject was relegated to a hopeless, incurable, museum-piece status. When one felt constrained to investigate more deeply, the fact that of all cardiac lesions congenital heart disease comprised but 2 to 3 per cent,[1] and of these cyanosis was present in but a relatively small number, the prospect of material contribution either clinical or technical seemed gloomy indeed. The attitude prevailed—"what is to be gained?" or "is it worth it in the final analysis?"

Such reasoning and concepts were almost immediately dispelled by the brilliant contributions of Blalock and Taussig in 1945, when the problems of cyanotic heart disease were reduced to a logical and salvagable sequence. Their initial endeavors were concerned with the mechanism whereby cyanosis was produced. They pointed out that in the common form of congenital cyanotic heart disease—the tetralogy of Fallot, embracing as it does the combination of pulmonary stenosis, dextroposition of the aorta, interventricular septal defect and right ventricular hypertrophy—the diminution of pulmonary blood flow was the dominant factor in the early demise of these infants. They had thereby reduced an anatomic malformation to its physiologic corollary. If, as it seemed at that time, it was impractical to correct the structural defects responsible for the reduction of pulmonary blood flow, it might well be feasible to counteract the result of these defects by the artificial establishment of new vascular pathways whereby unoxygenated blood might be rerouted through the pulmonary bed.

The ingenious, systemic-pulmonary shunt employing a subclavian artery-pulmonary artery anastomosis as devised by Blalock and Taussig[2] has become the standard operative method for the relief of the tetralogy of Fallot syndrome,

From the Department of Thoracic Surgery and the Department of Pediatrics of the Hahnemann Medical College and Hospital, Philadelphia, the Department of Thoracic Surgery and Department of Cardiology of St. Christopher's Hospital for Children, Philadelphia, and St. Michael's Hospital, Newark, N. J.

The experimental aspects of this project were partially supported by U. S. Public Health Grant H94.

Read at the Thirty-first Annual Meeting of the American Association for Thoracic Surgery, Atlantic City, N. J., April 16-18, 1951.

and its acceptance is universal. The equally ingenious modification of this procedure, the direct aortic-pulmonary artery anastomosis of Potts, Smith, and Gibson[3] has shared the acclaim afforded such shunts, and is also widely employed by surgeons in this country and abroad. As is well known, such extracardiac shunts essentially by-pass the intracardiac pulmonary obstruction, redirecting mixed venous-arterial aortic blood into the pulmonary vascular bed where its oxygenation effectively relieves the clinical signs and symptoms manifested by the now highly publicized "blue baby." Thus an additional (fifth) defect has been added to four already present, albeit one which in large measure overcomes the immediate and obvious effects of the condition under consideration. Nevertheless, a "patent ductus arteriosus" has been created, a defect which were it to be found in existence alone would demand, by present standards, early surgical correction. The late effects of such an arteriovenous fistula on the heart and circulation are well known, and, although the interventricular septal defect in the tetralogy may conceivably counteract in some measure the deleterious late effects of an artificially produced ductus, there is certainly cause for real concern as to the eventual fate of a patient harboring such a nest of dangerous anomalies.

Without detracting in the least from the excellent results achieved by extracardiac shunt procedures, it would seem entirely reasonable to redirect one's thinking from purely physiologic lines and to consider the problems posed by the underlying anatomic defects themselves. Is it possible to relieve the pulmonary obstruction by a more direct intracardiac approach and thereby reduce (and not increase) the number of defects with which the patient must contend? In order to effectively accomplish such an obviously desirable feat it is, of course, essential to obtain a thorough understanding of the nature of the pathologic obstruction in the pulmonary channel. Having ascertained and assessed the pathologic changes, means for rapid, safe, and efficient correction must be perfected. Initial results of such a new departure as would be embodied by a direct surgical approach must be at least comparable to those already obtained by shunt procedures, and the prospect that the patient will have a more nearly permanent relief and a more certain future must at least theoretically outweigh present doubt which exists concerning the eventual physical havoc that may result from the presence of a surgically-produced shunt.

In spite of the fact that a very large number of cyanotic patients with various types of pulmonary obstruction have been studied clinically and treated surgically, there is little detailed data available as to the relative incidence of the individual anatomic variances which may be present within the right ventricular outflow tract or at the root of the pulmonary artery. It is well established, however, that pulmonary stenosis, either valvular or infundibular, may exist as a single defect or more commonly be found in association with any combination of intracardiac anomalies, particularly those designated by the term tetralogy of Fallot. In this condition, infundibular stenosis, i.e., a muscular hypertrophy or fibrous malformation of the ventricular myocardium proximal to the pulmonary valve, rather than valvular, has been considered to be almost

invariably present. There is no doubt that some less common forms of infundibular stenosis almost defy direct surgical attack., On the other hand, others invite it, and certainly valvular stenosis is well suited to direct incisional separation. The crux of the situation simply stated would seem to be—how often is the stenosis valvular and how often is it infundibular? What forms does infundibular stenosis take? What is the nature of valvular stenosis? Can both be overcome surgically in a satisfactory manner with sufficient regularity to warrant the use of a direct approach routinely?

Brock[4] has devoted considerable energy to the study of the pulmonary artery-conus segment in cyanotic heart disease in the hope that clarification might lead to a direct and more logical approach. His findings and subsequent conclusions are brilliant examples of the very basic role played by exacting pathologic observation in the development of any new surgical procedure. He has described the following variations as depicted very diagrammatically in Fig. 1: (*a*), pure valvular stenosis, (*b*), a high degree of pulmonary artery hypoplasia with a bicuspid valve and stenosis lying immediately subvalvular in a narrowed muscular channel, (*c*), a high infundibular stenosis proximal to a relatively normal pulmonary artery and valve (the commonest type), and (*d*), a low infundibular stenosis at varying levels, creating a small or large infundibular chamber (third ventricle) proximal to a normal pulmonary artery and valve. The wall of this chamber may be either thin and fibrous or muscular in nature.

These observations, some obtained by direct examination of specimens and others gleaned from the existing literature, portray the over-all picture in generalities only but give no specific statistical data as to their incidence in a given number of cases. It is to be noted that of Brock's twenty-six cases of tetralogy of Fallot treated by the direct cardiac approach up to mid 1950,[5] fifteen were associated with valvular pulmonary stenosis, and eleven had an infundibular block to the pulmonary flow. There were three deaths in each group, an outstanding achievement at this early stage in the development of a new and revolutionary operation. He has stated that infundibular stenosis is more common than valvular stenosis in such cases, hence the incidence as recorded in these twenty-six cases cannot be taken at face value, for they were not consecutive cases.

A review of the early descriptions of Sandefort,[6] Corvisart,[7] Bartholemim,[8] Abernethy,[9] Farre,[10] Peacock,[11] Fallot,[12] and Keith[13] has shed no further light on the subject. Hope[14] described one case of tetralogy in an 8-year-old child whose pulmonary artery orifice was contracted "to the size of a goose quill," which is suggestive of a valvular stenosis. In Fallot's original papers[12] the first case showed a flattened and lengthened infundibulum forming a narrowed channel. The pulmonary artery was conical in shape with the base of the cone at its origin. The pulmonary cusps were fused and contained a small orifice. Keith[13] examined more than two hundred seventy cases of malformed hearts. One hundred forty-one of these were "imperfect because of a lesion connected with the transformation of the bulbus cordis (infundibulum) during the de-

velopment of the embryo." At least forty-seven of these, and probably a number more, had some degree of valvular stenosis. His material is not sufficiently detailed to allow a more accurate and exacting breakdown.

Selzer and Carnes[15] analyzed a group of twenty-eight autopsied patients who had survived more than fifteen years. Valvular stenosis was present in eight, hypoplastic pulmonary artery with two pulmonic cusps in seven cases, subvalvular stenosis was present in eight cases, and separate-conus-chamber type in one. The pulmonary artery was described as dilated in five cases, and was normal or hypoplastic in thirteen.

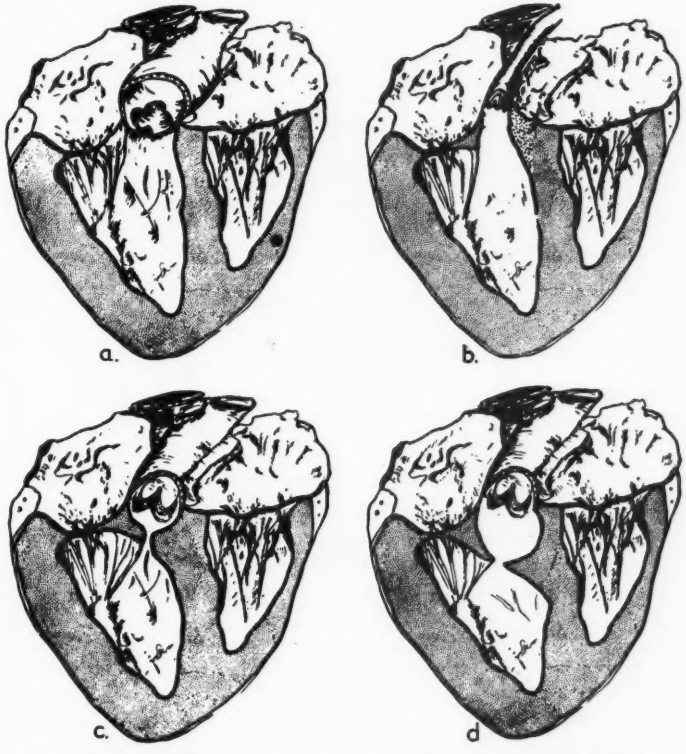


Fig. 1.—Types of pulmonary obstruction encountered in the tetralogy of Fallot: *a*, pure valvular stenosis; *b*, pulmonary artery hypoplasia with biscupid valve and subvalvular stenosis; *c*, high infundibular stenosis with normal valve; and *d*, low infundibular stenosis with normal valve. The other pathologic components of the tetralogy of Fallot are not shown (*b*, *c*, and *d*). (Reproduced by permission of J.A.M.A.)

Taussig,[16] Blalock and Kiefer,[17] Potts, Gibson, Riker, and Leininger,[18] Parker,[19] Edwards,[20] and others feel that in the majority of instances the pulmonary stenosis in the tetralogy of Fallot is in the pulmonary conus of the right ventricle, the infundibulum, rather than in the valve itself.

Doyen,[21] in 1913, was the first to attempt the direct relief of the pulmonary stenosis in the tetralogy of Fallot. His case had a subvalvular stenosis, and

did not survive the procedure. Sellors[22] was the first to revive the direct cardiac approach, and performed the first successful pulmonary valvulotomy on record. His patient was also suffering from bilateral pulmonary tuberculosis, and at last report was progressing satisfactorily in a sanatorium.

A complete review of the literature has not been included in this report, but will be the subject of a future communication.

At the onset of the present study herein reported, the authors were fully cognizant of the existing pathologic concepts and the prevailing opinion concerning these data. Nevertheless, it was considered feasible and altogether desirable to determine at first hand the practicability of employing direct intracardiac measures regardless of current impressions, no doubt prodded by a measure of success obtained in the surgical treatment of mitral stenosis acquired in the face of overwhelming odds based on time-honored pathologic and technical misconceptions.[23] This attitude was stimulated not a little by the recent visit of Brock to this country, and by his initial writings. The authors agreed, and it is still their opinion, that the pulmonary stenosis under consideration by embryologic design is primarily infundibular (development of bulbus cordis inclusive of the conus arteriosus). It is essential to remember, however, that the main pulmonary artery, the aorta and their contained valves, share in this developmental process. Every conceivable variation can occur, and indeed has been reported, so that malformations can exist in the muscular infundibulum, and/or the valves and/or the pulmonary artery singly or in combination. Perhaps in the majority of instances a measure of stenosis is present in the right ventricular outflow tract, but this narrowing is one of *degree* and may or may not play a part in the production of the clinical picture. The channel may be long and narrow throughout, or it may be constricted at *either end.* The channel may be quite adequate, although narrowed by normal standards, for the passage of blood with the obstructing factor localized in the valvular deformity or in the pulmonary artery itself. Only by observation and examination of the heart in the *living state* can these changes be fully appreciated from the functional standpoint. In the past, too many dictums have been proclaimed as the result of post-mortem examination which may be deceptive or represent extreme states, especially when death occurred at an early age. It must be realized that the heart as a whole and in part is a muscular walled tube undergoing marked variation in size with systole and diastole. Even though anatomically imperfect, only a part of this imperfection may be the underlying causative factor. Considerable experience with and direct scrutiny of the malformed area will be required before the exact pattern—anatomic and functional—can be properly evaluated and most effectively corrected.

TECHNICAL CONSIDERATIONS

The technique employed in this series is a modification of that originally described by Brock and by Sellors.

The patient is placed in the supine position and anesthetized. A left anterior submammary incision is used. This permits rhythmic inflation of both lungs without embarrassment to the operator in his intracardiac manipulations.

Great care must be taken with hemostasis, since the blood of these cyanotic individuals does not readily clot. In two of the cases it has been necessary to reopen the thorax to stop persistent bleeding from the edges of the pericardial incision and from the chest wall. The extensive vascularity of all tissues, particularly in older individuals with cyanotic heart disease, greatly aggravate this tendency to bleeding.

The third intercostal space is widely opened, the costal cartilages being fractured or cut, if necessary. The internal mammary vessels are divided between clamps and ligated. The left lung usually becomes slightly collapsed and remains out of the operator's field, even when partially inflated by positive pressure.

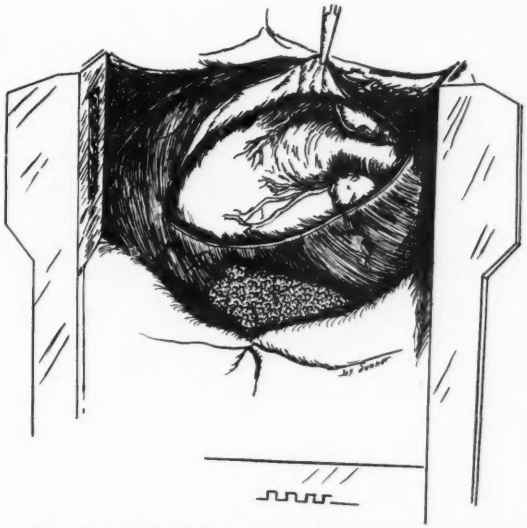


Fig. 2.—Fusiform dilatation of pulmonary artery with moderate constriction at its origin from right ventricle. Suggestive of valvular stenosis.

Care must be taken that the lower blade of the fixed rib spreader does not compress or traumatize the cardiac apex. The pericardium is picked up by a fine hemostat, one centimeter anterior to the left phrenic nerve, and incised. The incision is made parallel to the nerve, and extends superiorly over the pulmonary artery. It is advisable to limit the lower extent of this pericardial opening so as to preserve its protective action against overdistention of the ventricles, and to prevent a tendency to displacement of the heart out of the sac. However, one must have enough room to perform the essential maneuvers within the heart, and this may require extension of the pericardial incision to the diaphragm.

Several cotton or silk sutures are placed in the medial lip of the pericardial incision, and are attached to the rib spreader in such fashion that the sac is held open and the heart is somewhat rotated from its midline position toward

the left. This rotation brings more of the right ventricle into view, and the exposure may be increased by converting the original longitudinal opening into a L-shaped one by adding a medial extension at the lower extremity.

The field is now inspected and palpated in an attempt to make an exact anatomic diagnosis. A fusiform dilatation of the pulmonary artery with definite constriction at its origin from the right ventricle is almost pathognomonic of a true valvular stenosis (Fig. 2). Palpation of such a dilated vessel will reveal general flaccidity, or lack of tension, within it, except at the moment of cardiac systole. A systolic thrill is palpable over the vessel. In the young subjects with dilated pulmonary arteries, there has been noted a localized systolic bulge in the vessel wall, and at this point the thrill is most intense. In older patients this bulging is absent or minimal. Digital compression of the vessel from without,

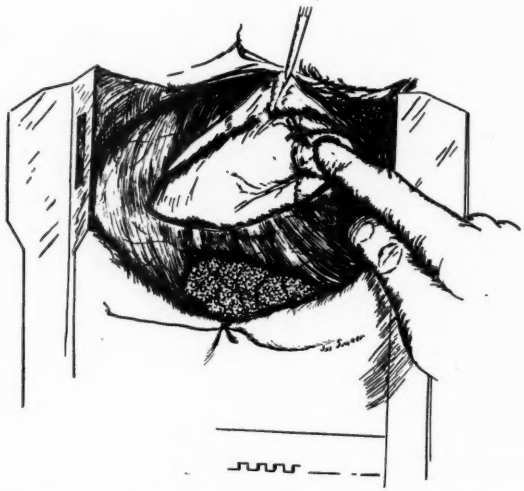


Fig. 3.—Digital compression of the pulmonary artery to determine the presence of valvular stenosis.

at this point, sometimes permits palpation of a small volcano-like structure at the cardiac end of the vessel. This erupts at each systole with a jet of blood from the heart. More vigorous pressure against the "crater" of this "volcano" completely prevents the entrance of blood into the artery and removes all trace of the thrill (Fig. 3). Because of the high interventricular septal defect, the right ventricle still has an adequate outlet and, therefore, is not immediately embarrassed either by this digital obstruction or by subsequent complete obstruction from within by dilating sounds. Sometimes, even in a well-developed pulmonary valvular stenosis, the artery is not enlarged, and occasionally may even be unusually small. In such a case there may be a high infundibular stenosis in the immediate subvalvular region. Such a high infundibular stenosis, alone or combined with a valvular stenosis, is probably not too uncommon, and

may have been present in a number of cases which we interpreted as being valvular. Such a defect would respond well to the usual treatment applied to the true valvular type, and so does not seriously complicate the surgical management.

In certain instances, fortunately rare in children more than 1 year of age, intrapericardial inspection will reveal a generally hypoplastic main pulmonary artery, or one with a stricture or coaretation at some point along its course. The thrill will then be felt along the course of the vessel distal only to the point of obstruction.

In cases of infundibular stenosis, which may make up approximately half of the cases seen after 1 year of age, the pulmonary artery is usually small.

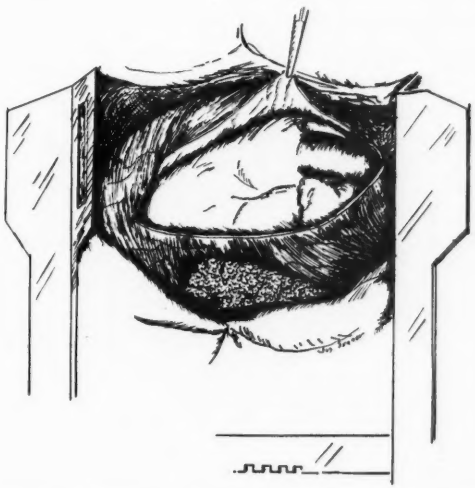


Fig. 4.—Variable sized bulge outlining the underlying infundibular chamber. Small vascular channels frequently overlie the segment of true constriction.

It may, however, fan out or funnel out slightly at its distal extremity. The thrill will be felt rather diffusely along the course, but will also usually be felt over the distal ventricle. This thrill over the ventricle tends to differentiate the condition from cases of valvular or arterial stenosis which do not present a thrill over the ventricle.

Sometimes a thin-walled infundibular chamber can be made out distal to an "isthmus" or waistlike narrowing of the right ventricle (Fig. 4). This may be a very small chamber varying from a pea to a cherry in size. Or it may be a sizeable structure, the size of an egg. In other cases it is just as thick and muscular as the true right ventricle. In such cases the diagnosis is less easily made by inspection. Even here, however, there may be a waistlike effect. Visible blood vessels running in a direction different from the course of the normal coronaries may outline this "waist" and its underlying septum (Fig. 4).

In no case should an opening be made into a thin-walled infundibular chamber, as the tissues may not be strong enough to hold reparative sutures. A muscular infundibular chamber may, however, be entered with impunity.

When a valvular stenosis is clearly present, or strongly suspected, we inject the anterior wall of the right ventricle with 0.5 per cent procaine solution to lessen the likelihood of producing a ventricular arrhythmia. Two transverse stay sutures of heavy silk are then inserted deeply into the myocardial wall so that it can be incised in a *transverse* direction about 2.5 cm. below the level of the valve. A very tiny transverse opening is then made, and a small urethral sound is inserted through it until it enters the ventricular chamber. Extreme care must be taken that this sound does not pass far beyond the endocardium, lest it pass below some of the papillary musculature attached in this region. It

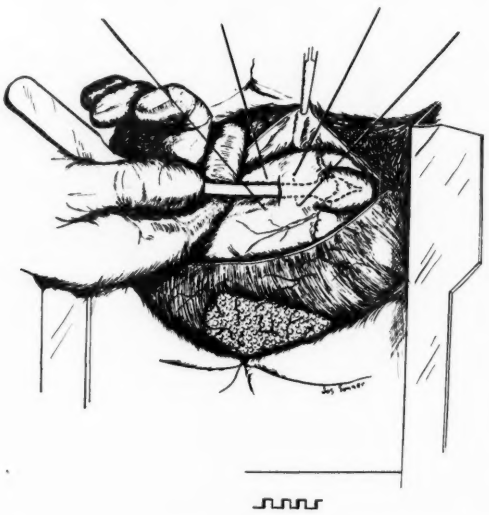


Fig. 5.—Malleable probe, or urethral sound, passed into and through the tiny valvular orifice.

is then directed up toward the valve and through it into the pulmonary artery. In a small child a No. 18 or 20 standard sound will usually become tightly gripped by the stenotic valvular orifice (Fig. 5). Having passed the sound through the valve, the direction for passing the valvulotome is established, since it can be bent in a curve similar to the sound. The sound is now withdrawn until its tip is close to the endocardial wall, and is redirected so that it may be passed down toward the apex of the right ventricle. Failure to meet intracardial obstruction rules out the presence of any significant infundibular septum. It is then passed up into the aorta if the diagnosis of tetralogy has not previously been established. If the operator is now satisfied as to the absence of an infundibular and the presence of a valvular stenosis, the sound is removed from the heart, and bleeding from the puncture wound is controlled by digital pres-

sure and traction on the stay sutures. If there remains any doubt as to the exact anatomic diagnosis, the myocardial incision is enlarged, and a finger of the left hand is inserted into the right ventricle. The little finger is chosen in children, but the index finger is more adept and, therefore, preferable in adults. It can be inserted through the pulmonary valve if not stenosed, through the high ventricular septal defect, and back to the tricuspid valve region of the ventricle. This method of digital intracardiac examination has much to commend it, and little but psychologic inhibitions to prevent its much wider application.

Having established the presence of a valvular stenosis, the operator will choose a suitable sized valvulotome of the Brock type. We prefer the so-called "universal valvulotome" (G. P. Pilling & Sons) because the flat malleable handle permits adjustment to various anatomic variations and causes less bleeding from the heart (Fig. 6). It is our practice to estimate the proper sized valvulotome with relation to size of the pulmonary artery at the level of the constricting ring. We then select the next smaller instrument. Failure to choose a smaller valvulotome than the exact estimated size once resulted in division of the entire thickness of the arterial wall as well as the valve ring.

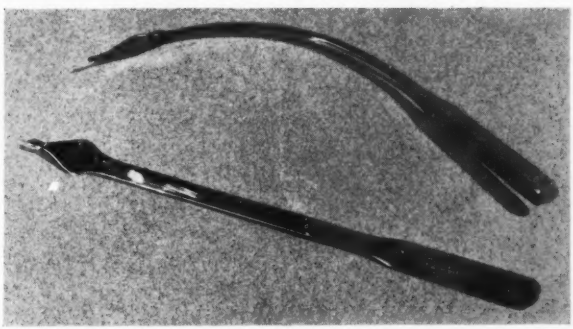


Fig. 6.—Flat malleable universal valvulotomes used for division of valvular stenosis. These can be molded to fit the conditions present in individual cases.

While such an inadvertent incision of the lateral or medial walls of the pulmonary artery may be readily sutured, unnecessary blood loss and additional risk to the patient is the natural result. The possibility of such an accident should moreover point the advisability of incising the valve in a horizontal plane. If the valvular division should be made in a vertical plane, the possibility of inadvertent injury to the posterior (inaccessible) wall of the artery, technically nearly impossible to suture, would be ever present.

Having chosen the valvulotome, it is inserted through the myocardial incision. Brock usually passes his knife so that the anterior myocardial opening is longitudinal, rotating the instrument ninety degrees after entering the cardiac chamber. We prefer to have the instrument enter the right ventricular chamber through a transverse myocardial incision since it then, by slight upward redirection as soon as it enters the chamber, is already in position to enter and

cut the pulmonary valve without danger of dividing a papillary muscle. The valvulotome is smoothly passed until the olivary tip seeks out and passes through the tiny apical valvular orifice. By further passage the somewhat cartilaginous resistance of the valve is overcome, and the instrument passes freely up into the lumen of the pulmonary artery where it becomes readily palpable through the anterior arterial wall (Fig. 7).

The instrument is then removed from the heart, and bleeding is controlled by digital pressure, perhaps with slight upward countertraction with the stay sutures. A few minutes should be permitted to elapse to observe the response to this maneuver. Then, we feel that *one* dilating instrument should be passed through the pulmonary valve to obtain the widest possible aperture without further rupture of the valve or vessel. Brock has a special dilator which he

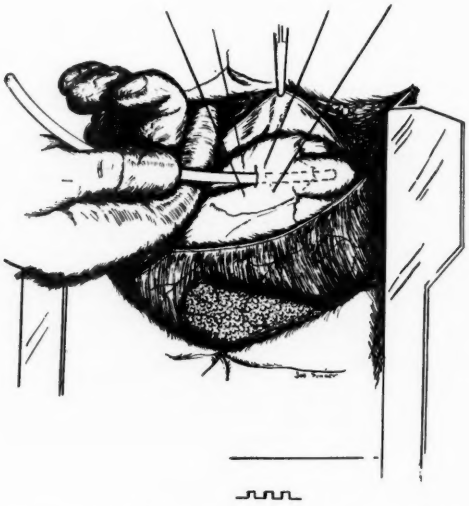


Fig. 7.—The valvulotome dividing the stenosed valvular cone into a biscupid valve.

recommends. An ordinary urethral sound of adequate size is most satisfactory in our hands. Probably the left little finger or the left index finger is the best of all dilating instruments at this stage, permitting tactile orientation and appreciation, as well as manual enlargement of the opening (Fig. 8).

After dilatation, the finger or instrument is removed from the heart, the stay sutures are crossed to control bleeding, and interrupted cross sutures are applied to approximate the cut muscular edges. The stay sutures may be tied or removed. The pericardium is reconstructed at least to cover the line of myocardial incision. Very careful hemostasis is employed in closing the chest because of the previously mentioned tendency to bleeding. The pleura is always drained by a No. 26 urethral catheter connected with a water-seal bottle.

The technique for the relief of an infundibular obstruction is, of course, significantly different from the foregoing but may be as satisfactory in suitable circumstances.

Having inspected and palpated the exposed heart, the operator should have a very definite opinion as to the probable existence of an infundibular stenosis, and an idea of the probable location of the septum. Stay sutures are applied into the wall of the myocardium as previously described to permit a *longitudinal* incision. Brock chose to enter the heart either well above or below the infundibular septum, so that his punch can be passed through the diminutive natural communication of the two chambers, to punch out a circular collar of tissue from the septum. We chose, on the other hand, to make our incision directly

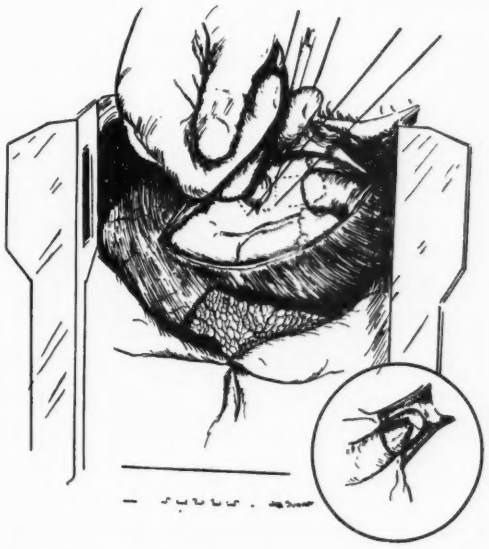


Fig. 8.—The left index finger, or largest urethral sound, passed through the divided valve to insure patency, not to produce additional dilatation or splitting.

over the infundibular septum so that we can bite or rongeur out a sizeable portion of it. Naturally, we take great pains not to extend any of the myocardial incision over a thin walled infundibular chamber which is sometimes present.

Usually a small knife puncture is made at the selected point, and a small urethral sound is inserted through it into the heart. By passing it successively up through the pulmonary valve, through the high septal defect into the aorta, and again down toward the apex of the ventricle, an idea of the nature of the obstruction can be obtained. Better yet, the left little finger, or even the index finger, may be inserted into the heart and passed successively in the same directions. Usually, one of two situations is found. There is either a high sub-

valvular membranous stenosis, or there is a transverse muscular septum at a lower level, and usually it is immediately under the middle of the myocardial incision if that has been correctly placed.

In the former instance (high stenosis), while the finger is in place, the proper sized flat-handled valvulotome may be passed alongside the finger and up through the obstruction out into the pulmonary artery in a manner similar to that used for valvular stenosis, but this time guided by the intracardiac finger. After dividing the stenosis, the instrument is removed and the finger is passed up into the pulmonary artery as a dilator.

In the lower infundibular stenosis the exploring intracardiac sound or, preferably, finger reveals the transverse muscular septum. If the myocardial incision is directly over it, it may be extended to better straddle the septum. A pair of modified bone rongeurs (Fig. 9) is then plunged into the heart, jaws open to engage the septum. A good-sized bite of tissue is thus removed, usually widely interrupting the continuity of the obstructing septal wall (Fig. 10).

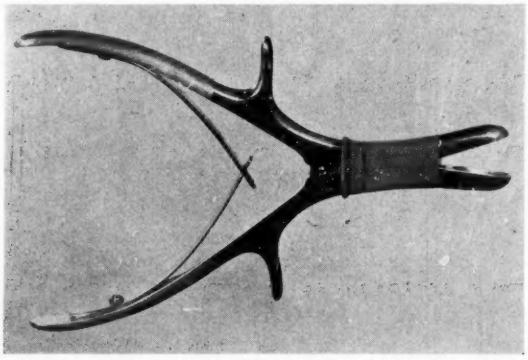


Fig. 9.—Small double-action rongeur with sharp cutting edges and deeply umbilicated to hold the resected specimen.

The use of this ronguer is most suitable in older children or adults. In infants and small children we prefer a small-sized pituitary forceps as suggested by one of us (D. F. D.). The operator's finger controls bleeding from the heart just before and after the rongeurs are inserted. It may be considered necessary to remove a second bite of septal tissue in the same way. The finger now momentarily re-enters the heart, to reveal complete continuity of the infundibular and true right ventricular chamber. The stay sutures are crossed and the myocardial incision is closed as previously described in the valvular case.

In the case with extreme hypoplasia or atresia of the pulmonary artery, no direct relief of the obstruction will be possible. Such cases must always be treated by either a Blalock-Taussig or a Potts-Gibson systemic artery-pulmonary artery anastomosis. However, there are some cases in which the pulmonary artery at the level of the valve seems to be of normal size. About a centimeter above the valve the vessel becomes abruptly narrower like an aortic coarctation,

only to again become normally large at the level of its bifurcation. The thrill in such cases is felt in the artery distal to the stricture. This condition may be treated by passing successively larger sounds through the stenosed area until it is felt that blood flow has been substantially increased. The same type of myocardial incision is used as has been outlined.

ANALYSIS OF CASES

An analysis of thirty consecutive cases of tetralogy of Fallot treated surgically by the direct intracardiac approach forms the basis of this report. Not included are our cases of "pure" pulmonary stenosis, usually valvular, in which there is an intact interventricular septum without overriding of the aorta. A separate report of this series will be presented in the near future.

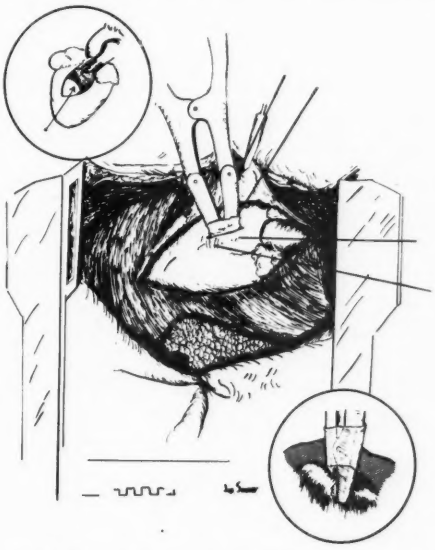


Fig. 10.—The rongeur in place showing method of resection of a portion of the infundibular ridge.

As a group, these patients exhibited all of the classical clinical features of the often-described tetralogy of Fallot. Easy fatigue, cyanosis of the lips and nail beds, exaggerated by physical activity, clubbing, and dyspnea on the slightest exertion, were characteristic. In addition to the usual clinical findings, electrocardiographic pattern, fluoroscopic and roentgen picture, the diagnosis in twenty-four of the thirty was confirmed preoperatively by the angiographic demonstration of immediate and simultaneous opacification of the aorta and right ventricle. In four of the remaining six (Cases 8, 16, 20, 22, 23, 28) the study was attempted but proved unsatisfactory. The diagnosis in these cases was verified at the time of surgery by direct observation or by the passage of a probe through the ventricular septal defect into the aorta from the right ventricle. The first eight cases have been published in abstract elsewhere.[24]

TABLE I. CASES OF TETRALOGY OF FALLOT TREATED BY DIRECT INTRACARDIAC SURGERY

CASE	AGE AND SEX	TYPE OPERATION	DATE OPERATION	TYPE STENOSIS	AORTIC ARCH	HBG.—R.B.C. (PREOP.)		HBG.—R.B.C. (POSTOP.—OVER 6 MO.)		RESULTS TO DATE
1. M. B.	3—F	valvulotomy	12-7-49	valvular	L	19.0	8.7	15.0	5.1	excellent
2. K. K.	3—M	dilatation	2-3-50	infundibular	L	16.7	5.6	13.9	4.9	very good
3. D. J.	4—F	resection	2-7-50	infundibular	R	16.4	5.6	11.8	4.5	excellent
4. H. C.	12—M	valvulotomy	3-10-50	valvular	L	16.2	5.5	11.1	3.9	excellent
5. M. R.	18—F	valvulotomy	3-29-50	valvular	L	15.0	4.7	12.0	3.8	died 2½ mo. (transfusion reaction)
6. L. F.	3—M	resection	4-12-50	infundibular	L	16.0	5.3	12.5	4.2	very good
7. R. B.	6—M	valvulotomy	4-26-50	valvular	R	14.5	4.3	11.5	3.9	very good
8. A. S.	21—F	resection	5-3-50	infundibular	R	18.0	7.4	14.0	4.8	excellent
9. W. B.	2—M	resection	7-24-50	infundibular	R	12.2	5.4	11.7	4.0	excellent
10. T. P.	16—F	valvulotomy	8-23-50	valvular	L	18.6	6.6			very good
11. C. P.	2—F	dilatation	8-28-50	pul. art. sten.	L	11.8	6.6	13.0	4.4	excellent
12. M. O.	2—F	attempted resection	9-26-50	infundibular	L	15.9	7.0			died on table (trauma and hemorrhage)
13. E. U.	4—M	valvulotomy	9-28-50	valvular	L	15.2	5.3	10.7	5.6	excellent
14. R. D	5—M	dilatation	10-11-50	pul. art. sten.	L	16.0	6.1	13.0	3.8	excellent
15. B. H.	4—F	attempted resection	10-23-50	infundibular	R	16.9	5.8			died on table (cardiac arrest)
16. D. B.	21—M	valvulotomy	10-25-50	valvular	L	10.0+	5.3	76%	4.3	very good
17. E. K.	12—F	valvulotomy	10-28-50	valvular	R	17.7	5.5			excellent
18. S. H.	2—F	valvulotomy	11-3-50	valvular	L	18.6	5.7			died on table (cardiac arrest)
19. W. B.	2 mo.—M	valvulotomy	11-8-50	valvular	L	17.0	6.7			died—6 hr. (postop.?)
20. R. H.	15—M	dilatation	11-15-50	pul. art. sten.	L	18.0	8.8			excellent
21. W. G.	2—M	attempted resection	11-20-50	infundibular	L	14.9	4.9			died on table (cardiac arrest)
22. K. S.	2—F	resection	11-23-50	infundibular	L	17.7	7.4			very good
23. S. B.	36—M	dilatation	11-29-50	valvular	L	18.0	7.0			very good
24. J. G.	22—M	valvulotomy	11-22-50	valvular	L	18.6	6.9			very good
25. W. C.	31—M	attempted dilatation	2-28-51	infundibular	L	16.9	6.1			died on table (tracheal obst.—anesthesia)
26. R. M.	15—M	valvulotomy	3-14-51	valvular	R	16.5	5.9			excellent
27. J. W.	21—M	valvulotomy	3-14-51	valvular	L	16.0	6.3			excellent
28. L. K.	12—F	valvulotomy	3-28-51	valvular	R	15.0	5.5			too recent for evaluation
29. M. F.	14—F	valvulotomy	3-28-51	infundibular (subvalvular)	L	83%	4.3			too recent for evaluation
30. D. S.	4—M	resection	4-9-51	infundibular	L	11.1	4.8			too recent for evaluation

Protocols of the more recent cases are similar in type except for the usual individual variations and will not be enlarged upon here. Table I contains the essential data in each instance.

VALVULAR STENOSIS

Surprisingly, in fifteen (50 per cent) of the group, ready egress of blood flow from the right ventricle was obstructed by *stenosis of the pulmonary valve,* a much higher incidence than has been presumed to occur in this combination of defects.

The presence of a valvular stenosis could not be predicted preoperatively with certainty. Their preoperative clinical course did not vary appreciably from the group as a whole. The position or character of the usual systolic murmur over the precordium was not diagnostic. Laboratory studies shed no light as to the type of pulmonary block. Catheterization studies done in a few yielded high pressures (50 to 80 mm. Hg) in the right ventricle and low pressures in the pulmonary artery (5 to 30 mm. Hg) when entered. The site of obstruction could not be accurately determined by observing the passage of the catheter in its course through the right ventricle fluoroscopically.

Angiocardiographic examination was perhaps of greater value than all other studies combined. As a rule, although not invariably true, the presence of valvular stenosis could be strongly suspected by the demonstration of a large pulmonary artery in which the diodrast tended to "hang up" throughout the entire study on successive films (six to eight seconds). Post stenotic dilatation of the pulmonary artery was observed but not with the frequency and clear delineation frequently seen in "pure" pulmonary stenosis with intact ventricular septum.

Direct inspection and palpation of the heart and great vessels through the open pericardium at the time of surgery provided the most definitive answer as would be expected although in several instances even this examination left some doubt as to the exact nature and location of the obstructing deformity (see above, under technique).

The average age at the time of surgery in this group was 13 years, the oldest patient being 36 years, and the youngest 2 months. Nine were males and six females. There was a normal left aortic arch in eleven, right aortic arch in four.

The results obtained could not have been more dramatically divergent. These patients either did beautifully or did not survive. Six were obviously *excellent,* and this was apparent within a short time after surgery. Their present activities are *unlimited* and, except for a faint, scarcely noticeable (to the suspicious observer) bluish tinge to the mucous membranes of the mouth after vigorous exercise, they have no cyanosis. Five are regarded as *very good.* These cannot quite carry on complete normal activity in all its phases for their individual age group. As the lapse of time from the date of surgery in the oldest of these is slightly under a year, there is every reason to believe that

too recent for evaluation
L 11.1 4.8
infundibular
4-9-51
4—M resection
30. D. S.

further improvement can be expected. One additional case (Case 28) is progressing exceptionally well at this time, but an insufficient period has elapsed to warrant classification of the result.

There were two operative deaths. In the first (Case 18), a child of 2 years, the pulmonary artery was found to be very small. Cardiac action deteriorated as the pericardium was opened. It was feared that the insertion of a Brock knife into this small pulmonary artery could not be accomplished with safety. Accordingly, a dilating sound was inserted through the stenosed valve. Cardiac action ceased and, in spite of vigorous resuscitative measures, the child died.

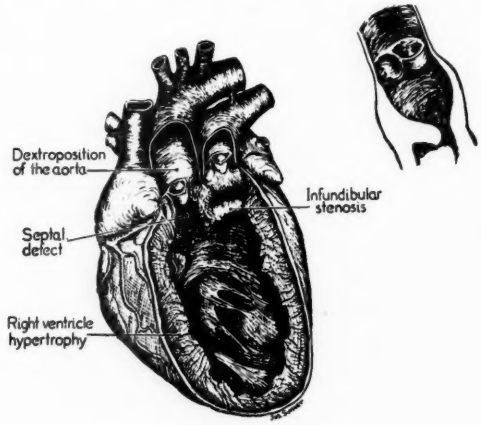


Fig. 11.—High infundibular stenosis with grape-sized infundibular chamber proximal to a normal valve. (Drawn from specimen.)

The second patient (Case 19) was a 2-month-old infant with hydrocephalus. The pulmonary artery was somewhat smaller than normal. A valvulotomy was performed, and the infant's color became pink almost immediately. The entire procedure from skin to skin required only twenty-five minutes. Only 10 c.c. of blood were lost. About one hour postoperatively he exhibited some respiration distress. He was bronchoscoped, and a small amount of mucus was aspirated. Thereafter, his condition was eminently satisfactory for five hours. Then, suddenly, over the course of ten minutes, he deteriorated. Cardiac action was strong, the lungs were clear, and there was no obstruction to the airway which could be demonstrated bronchoscopically. Nevertheless, his respirations became weaker and weaker, and finally ceased. Autopsy was limited to the heart. It was found that the stenosed pulmonary valve had been converted into a bicuspid valve, and an adequate lumen existed. It is hypothesized that, in view of the hydrocephalus, the infant died of central causes.

A third patient (Case 5) died thirteen weeks postoperatively. Her demise was directly attributable to a blood transfusion reaction following a second operation, but it must be attributed ultimately to the initial pulmonary val-

vulotomy. Following incision of the valve, too large a sound was passed into the pulmonary artery. Pulmonary and tricuspid insufficiency became severe, and several weeks postoperatively plication of the pulmonary artery in the region of the valve was accomplished in an effort to decrease the lumen. A severe transfusion reaction occurred postoperatively and, after a stormy course of ten days, the patient died.

INFUNDIBULAR STENOSIS

An obstructing malformation of the pulmonary conus area (infundibulum) was present in twelve instances. For the most part the distortion of the right ventricular outflow tract followed a set pattern, although it varied sufficiently to permit classification into four categories based primarily on the size of the infundibular chamber and the position of the obstructing tissue.

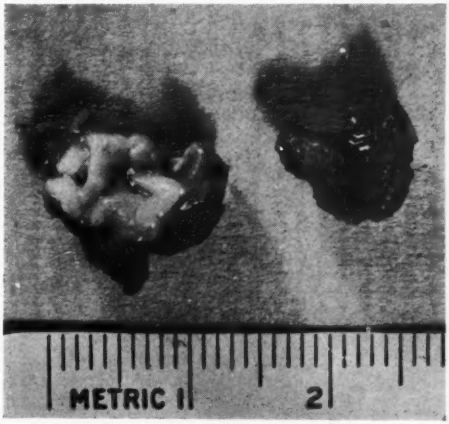


Fig. 12.—Type of specimen removed by rongeur resection. To the left, a portion of muscular ridge and overlying endocardium at the infundibular orifice. To the right an additional section of muscular septum removed to insure complete patency. (Photographed from specimen.)

1. Six cases (50 per cent) in this group were of the common type designated in Brock's classification above (Fig. 11). These had a high infundibular stenosis with a grape-sized infundibular chamber proximal to a normal valve. (Cases 2, 3, 6, 8, 15, 21). The point of muscular and fibrous obstruction was narrow, and lent itself readily to resection (Fig. 12). Two of the four patients in the infundibular series who died had this type of obstruction, and are commented upon below.

2. Three cases were subvalvular in type, and were so immediately proximal to the valve that differentiation from true valvular pathology was difficult (Cases 9, 22, 29). Two were resected and one was opened with the valvulotome after the manner used in valvular stenosis (Fig. 13). There were no deaths.

3. In two cases there was a high degree of pulmonary artery hypoplasia with a long, narrow muscular channel proximal to a split-pea sized subvalvular

chamber (Cases 12, 25). This type is by far the most difficult problem to be overcome by the direct intracardiac approach (Fig. 13). Resection was attempted in one, and manual dilatation in the other, both unsuccessfully.

4. In the remaining case (Case 30) there was a lower infundibular stenosis with a walnut-sized chamber proximal to a normal pulmonary valve. The stenotic area was narrow, and resection was readily accomplished by the usual rongeur technique.

As in the case with valvular stenosis, the classical clinical features of the tetralogy of Fallot were present in each, but again no clue as to the basic pathologic anatomy was suggested by clinical methods. Angiocardiograms provided the best presumptive evidence of the infundibular nature of the obstruction. The pulmonary artery was either of small normal or definitely diminished size. Not infrequently a suggestive gap or narrowing existed between the main body of dye accumulated in the right ventricle and the pulmonary artery. Too

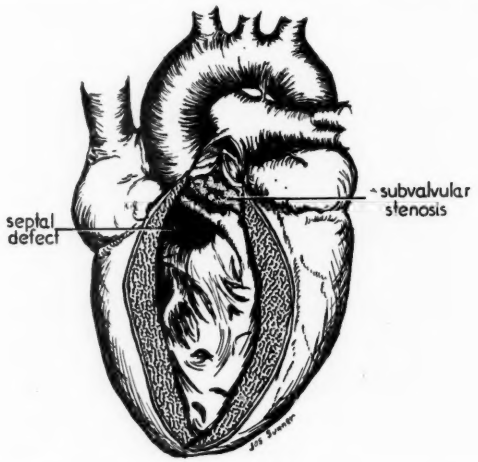


Fig. 13.—Subvalvular stenosis immediate proximal to the pulmonary valve. (Drawn from a specimen.)

often, however, this area was partially obscured by dye in the root of the dextroposed aorta so that definitive evaluation of the infundibular changes could not be made.

Again surgical exploration seemed essential to a true understanding of the condition present. Inspection and gentle palpation can usually determine the presence of infundibular changes as differentiated from valvular, but often the exact site of the occluded area can only be determined with accuracy by the exploring intraventricular probe (see technique above) or finger.

The average age at the time of surgery in this group was 5 years, the oldest 21 and the youngest 2 years. It is possible that the striking age difference between the infundibular and valvular cases in this consecutive series may be of some preoperative significance diagnostically. It suggests that the prognosis

of the infundibular patient is the poorer, and that fewer live to an age where the best surgical result can be obtained because of their more complicated malformations. This thought is not borne out, however, by analysis of Brock's series, although his cases were selected rather than consecutive. Six were males, and an equal number females. There was a normal left aortic arch in eight, right aortic arch in four.

There were four operative deaths. In the first (Case 12), a girl of 2 years, the heart slowed and stopped as the pericardium was opened. After five minutes of rhythmic manual contractions fortified by a small intracardiac injection of adrenalin and atropine, a vigorous heartbeat was restored. The pulmonary artery was quite small, the branch to the left lung being greatly atrophic. The usual myocardial incision was made, one bite taken from the muscular obstruction with difficult and more than average manipulation and blood loss. Heart contractions ceased as the myocardial incision was being sutured. Efforts

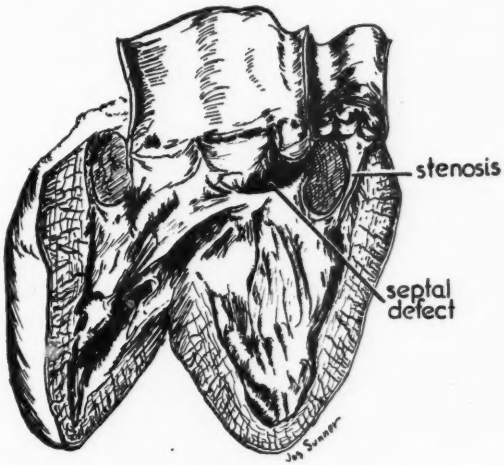


Fig. 14.—High degree of pulmonary hypoplasia with a long narrow muscular channel proximal to a split-pea sized subvalvular chamber. (Drawn from specimen.)

toward resuscitation were ineffective. Post-mortem examination of the heart revealed an infundibular muscular channel with a very tiny chamber proximal to a normal valve (Fig. 14). In all probability this type will be most difficult to relieve directly by methods now in use. A shunt procedure could not have been performed on the left in this case.

Case 15, aged 4 years, was a girl who had multiple and severe congenital anomalies in addition to her cardiac malformations. She was deaf, mentally deficient, and had peculiar bony deformation of her rib cage. The pulmonary artery was soft, flabby, and of normal size. A jet could be felt on the anterior surface of the pulmonary artery, even though the obstruction was infundibular. A bite was attempted by rongeur, but little was removed. A second bite seemed more satisfactory, and the myocardium was sutured. The heart slowed, but

vigorous action returned shortly. Examination failed to indicate improved blood flow in the pulmonary artery. The incision was reopened, two more bites taken, and the incision closed. Irreversible cardiac arrest ensued. Examination of the specimen revealed that, although adequate tissue had been removed, if properly taken, the obstructing ridge still remained intact (Fig. 15). There was a bicuspid valve partially stenosed.

The third patient (Case 21), a boy aged 2 years, was in a very precarious condition, and the operation was performed as a semi-emergency. This patient was deaf, dumb, and blind, with microphthalmia and microcephalia. The pulmonary artery was small, and a slight thrill could be felt on its anterior surface and over the distal portion of the pulmonary conus. The myocardium was opened directly over the obstructing infundibular ridge, an adequate bite was removed in the right place, and the wound closed (Fig. 16). The procedure was carried out with dispatch with only average trauma and blood loss. Within a minute the heart stopped and could not be revived. It is possible that the cerebral changes in this patient could not tolerate this or any other type of surgery. Examination revealed that a proper bite had been taken. There was an adequately functioning bicuspid valve.

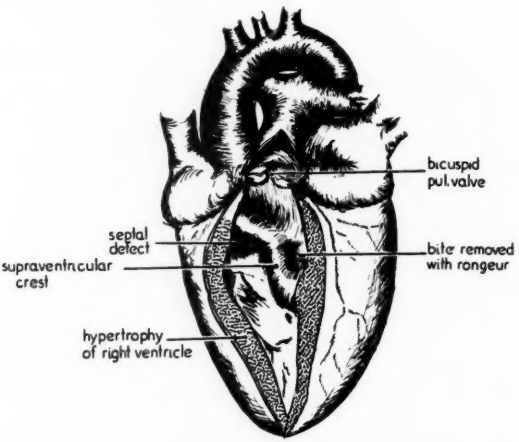


Fig. 15.—A resection of infundibular taken erroneously proximal to supraventricular crest. (Drawn from specimen.)

The last patient (Case 25) was a boy, aged 4 years, in reasonably good condition. The pulmonary artery was small, and a soft thrill could be felt over it and the distal ventricular outflow tract. The nature of the infundibular obstruction was confusing. The myocardial incision was made over the narrowed muscular channel, and a finger inserted to dilate the long narrow channel. The opening was felt to give and partially split in a stellate manner. The incision was closed, the heart slowed. Gentle massage quickly restored a normal beat and the chest was partially closed. Difficulty in maintaining adequate respira-

tory exchange was experienced, and shortly thereafter the heart stopped and could not be revived. A complete plug was found blocking the intratracheal tube. Examination of the specimen revealed that the dilatation had been off center, and a split had been made in the ventricular septum (Fig. 17).

STENOSIS OF THE PULMONARY ARTERY

There were three cases in which a localized constriction occurred in the main pulmonary artery distal to a normal pulmonary valve but proximal to the

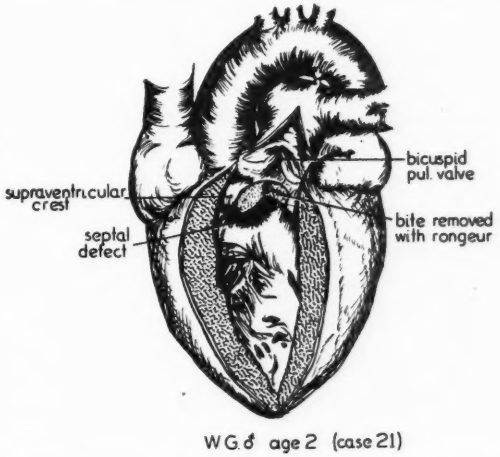


Fig. 16.—An adequate resection of a portion of the infundibular ridgelike obstruction. (Drawn from specimen.)

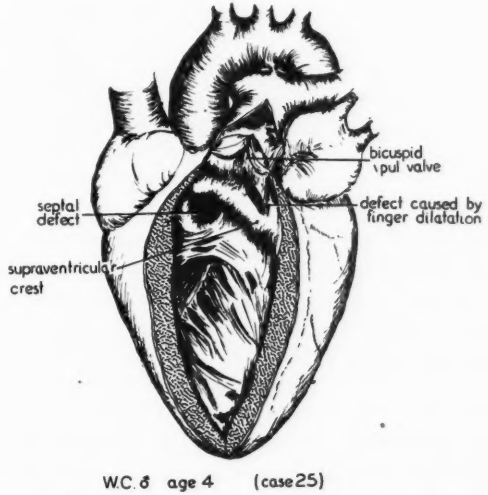


Fig. 17.—Digital dilatation splitting in infundibular tissue in the wrong area leaving the supraventricular crest intact. (Drawn from specimen.)

bifurcation of this vessel into its right and left major branches (Cases 11, 14, 20) (Fig. 18). These patients presented the identical clinical picture of the other patients in this series, nor were there any points of variation in their routine diagnostic studies. An angiocardiogram was successful in only two of the three in this group. The pulmonary artery appeared small in both, and no suggestion of the constriction found at surgery could be detected in it either preoperatively or at re-examination after surgery.

Direct inspection and probing of the ventricular outflow tract and pulmonary valve at the time of surgery failed to reveal any evidence of significant obstruction to the flow of blood except in the localized area as described above. The introduction of graduated sounds seemed to accomplish a most satisfactory enlargement of the arterial lumen. The eventual fate of a dilatation procedure such as this must await the verification of time.

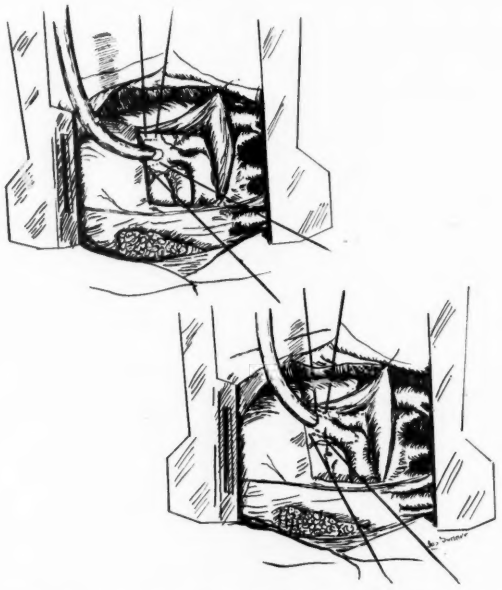


Fig. 18.—Localized constriction of the main pulmonary artery distal to a normal pulmonary valve. The method of dilatation employing graduated urethral sounds.

The average age at the time of surgery in this group was 7 years, the patients being 2, 5, and 15 years, respectively. Two were boys, one a girl. In each there was a normal left aortic arch.

DISCUSSION

In these thirty cases there were seven deaths, a mortality rate of 23.3 per cent. One death (Case 5) occurred thirteen weeks postoperatively, as described above, so that the actual operative mortality was 20 per cent. In the valvular group the mortality was 20 per cent, but if Case 5 is not considered an operative

death, the rate drops to 13.3 per cent. The mortality in the infundibular group was 33.3 per cent. There were no deaths in the three cases with localized stenosis of the pulmonary artery.

This mortality rate, although high, is quite in keeping with the early results obtained with anastomotic procedures. Blalock[25] reported an over-all mortality of 22 per cent in the first one hundred forty-four patients, with a diagnosis of pulmonic stenosis subjected to the production of systemic artery-pulmonary artery shunt. It is reasonable to assume that a material reduction in this initial rate will be brought about as further experience in the selection of cases and in the operative technique is gained; just as it has in the extracardiac procedures.

Many of the difficulties encountered in the intra- and postoperative management of these cases have been and will further be resolved as additional experience is gained. The most disconcerting intraoperative complication has been cardiac arrest. This occurred in twelve patients (Cases 2, 3, 8, 12, 15, 18, 21, 22, 23, 25, 25, 29). Eight of these recovered through the use of proper measures, and some now demonstrate the most satisfactory clinical response in the series. Of the four who did not recover, two had associated severe cerebral anomalies; it is recognized that such patients as a rule withstand any type of surgery poorly. The relatively high incidence of this serious complication is probably due to the following factors: (1) improper technique; the surgeon was hampered by his lack of knowledge as to the exact anatomical situation, or, although this had been determined, he was overeager in his manipulations, with resultant overwhelming trauma to the heart; and (2) the patients were not chosen with regard to their suitability for any operation; they were chosen because they had the tetralogy of Fallot and could be helped by operation—that was the single criterion.

One case of cardiac arrest may be cited as being of particular interest. This was the oldest patient in the group (Case 23). Exposure of the pericardium was delayed because of the necessity of clamping and ligating innumerable dilated vessels in the thoracic wall. The pericardium itself was covered by a network of dilated, tortuous vessels. As it was being opened, cardiac arrest occurred. Despite this, a myocardial incision was made. The valve was quickly dilated manually and with sounds. The myocardial incision was sutured and alternate manual compression, and release of the heart instituted. Adrenalin and atropine were administered into the ventricle. Myocardial tone improved and a spontaneous beat was established. Ventricular fibrillation ensued. Electric shock (110 volts alternating current) caused a severe tetanic convulsion and cardiac arrest. The heart then spontaneously resumed a normal rhythm. The total duration from the initial arrest to resumption of normal rhythm was nine minutes. Four and one-half hours after his return to the ward there was such brisk hemorrhage through the drainage tube that he was brought back to the operating room and his chest reopened. Innumerable bleeding points in pericardium and thoracic wall were ligated or

cauterized. His subsequent course was marked by aphasia and a right foot drop. Both improved steadily, and although there still remains some verbal difficulty he may be considered to have derived remarkable benefit from surgery.

In the immediate postoperative period, the most challenging complication has been the development of signs of cardiac failure. This occurred in eight patients (Cases 2, 3, 5, 6, 7, 8, 22, 24).

Each of these individuals, with one exception (Case 2), was either allowed ambulation or assumed the privilege before one week had elapsed. While the principle of early ambulation is accepted after most surgical procedures, it is not to be recommended when a cardiac chamber has been entered via a myocardial incision. We now feel that a period of at least two weeks should lapse before the patient is allowed any but minimal activity.

Minor pleural effusions have been encountered but have not posed a special problem.

In spite of the disappointing results in some patients and the complications encountered in others, it must be concluded that the direct intracardiac approach to the problem of pulmonary stenosis, whether it be pure or a part of tetralogy of Fallot, would appear to be sound and logical from both the anatomic and physiologic standpoints. There are some cases which, because of their nature, will require a shunt, but these should be determined only after thorough intrapericardial assessment of the anatomic situation.

SUMMARY AND CONCLUSIONS

1. Our total experience with the direct intracardiac relief of pulmonary stenosis in the tetralogy of Fallot has been presented. Thirty consecutive cases over a period of sixteen months have been analyzed.

2. Representative literature pertaining to the various types of pulmonary obstruction which may occur in the tetralogy of Fallot has been reviewed. Information concerning the relative incidence of infundibular and valvular stenosis is scant. Of thirty consecutive cases of tetralogy of Fallot, reported herein, the pulmonary stenosis in fifteen was thought to be valvular, infundibular in twelve, and localized to the pulmonary artery in three.

3. The technique of the direct intracardiac approach for each type of pulmonary obstruction has been presented, and the results assessed.

4. It has been pointed out that the currently accepted anastomotic procedures for the relief of pulmonary stenosis in the tetralogy of Fallot are attended by certain dangers because an additional vascular defect has been produced. The direct approach, if it be technically feasible, would appear to offer a more satisfactory long-term solution to the problem.

REFERENCES

1. White, P. D.: Chronic Valvular Disease in Textbook of Medicine, ed. 4, edited by Russel L. Cecil, Philadelphia, 1937, W. B. Saunders Co.
2. Blalock, A., and Taussig, H. B.: The Surgical Treatment of Malformations of the Heart in Which There Is Pulmonary Stenosis or Pulmonary Atresia. J. A. M. A. **128**: 189, 1945.

3. Potts, W. J., Smith, S., and Gibson, S.: Anastomosis of the Aorta to a Pulmonary Artery for Certain Types of Congenital Heart Disease, J. A. M. A. **132**: 627-631, 1946.
4. Brock, R. C.: Pulmonary Valvulotomy for Relief of Congenital Pulmonary Stenosis, Brit. M. J. **1**: 1121, 1948.
5. Brock, R. C., and Campbell, M.: Valvulotomy for Pulmonary Valvular Stenosis, Brit. Heart J. **12**: 377-402, 1950.
Infundibular Resection or Dilatation for Infundibular Stenosis, Brit. Heart J. **12**: 403-424, 1950.
6. Sandefort, E.: Observations Anatomico—Pathological, Lugd. Bat. P.V.D. Eyk et D. Vygh. 1777, Cop. 1, Fig. 1.
7. Corvisart (Quoted by Hope, J.): See reference 14.
8. Bartholemim (Quoted by Hope, J.): See reference 14.
9. Abernethy (Quoted by Hope, J.): See reference 14.
10. Farre (Quoted by Hope, J.): See reference 14.
11. Peacock, T. B.: Malformations of the Heart, ed. 2, London, 1866.
12. Fallot, A.: Contribution a l'anatomie pathologique de la Maladie bleue (cyanose carduique), Marseille méd. **25**: 77, 138, 207, 270, 341, 403, 1888.
13. Keith, Arthur: The Hunterian Lectures on Malformations of the Heart, Lancet, pp. 359-363, August 7, 1909.
14. Hope, J.: Treatise on Diseases of Heart and Great Vessels and on the Affections Which May Be Mistaken for Them, Philadelphia, 1846, Lea & Banchard, pp. 459.
15. Selzer, A., and Carnes, W. H.: The Types of Pulmonary Stenosis and Their Clinical Recognition, Mod. Concepts Cardiovas. Dis. **18**: 45-46, 1949.
16. Taussig, H. B.: Congenital Malformations of the Heart, New York, 1947, Commonwealth Fund.
17. Blalock, A., and Kiefer: Valvulotomy for the Relief of Congenital Valvular Pulmonic Stenosis With Intact Ventricular Septum, Ann. Surg. **132**: 496, 1950.
18. Potts, W. J., Gibson, S., Riker, W. L., and Leininger, C. R.: Congenital Pulmonary Stenosis With Intact Ventricular Septum. J. A. M. A. **144**: 8-12, 1950.
19. Parker, R. L.: Pulmonary Stenosis in Tetralogy of Fallot, M. Clin. North America **32**: 855, 1948.
20. Edwards, J. E.: Congenital Cardiac Disease, A Pathological Review, Post-Grad. M. J. **3**: 327-341, 1948.
21. Doyen, E.: Chirugie des malformations congenitales ou acquises du coeur. Presse med. **21**: 860, 1913.
22. Sellors, T. H.: Surgery of Pulmonic Stenosis, Lancet **1**: 988-989, 1948.
23. (a) Bailey, C. P.: The Surgical Treatment of Mitral Stenosis (Mitral Commissurotomy). Dis. Chest. **15**: 377, 1949.
(b) Bailey, C. P., Glover, R. P., and O'Neill, T. J. E.: The Surgery of Mitral Stenosis, J. THORACIC SURG. **19**: 16, 1950.
(c) Glover, R. P., O'Neill, T. J. E., and Bailey, C. P.: Commissurotomy for Mitral Stenosis, Circulation **1**: 329, 1950.
(d) Glover, R. P., Bailey, C. P., and O'Neill, T. J. E.: Surgery of Stenotic Valvular Diseases of the Heart, J. A. M. A. **144**: 1049-1057, 1950.
(e) O'Neill, T. J. E., Glover, R. P., and Bailey, C. P.: Commissurotomy for Mitral Stenosis, J. Internat. Col. Surg. **13**: 355. 1950.
24. Downing, D., Bailey, C. P., and Glover, R. P.: The Brock Procedure for the Relief of Pulmonary Stenosis in Tetralogy of Fallot, Pediatrics. **7**: 230, 1951.
25. Blalock, A.: The Technique of an Artificial Ductus Arteriosus in the Treatment of Pulmonic Stenosis, J. THORACIC SURG. **16**: 244-257, 1949.

DISCUSSION

DR. WILLIS J. POTTS, Chicago.—Dr. Glover would be disappointed if we did not discuss this paper. In speaking of pulmonary stenosis, we must very definitely differentiate between the two distinct types; pulmonary stenosis with intact intraventricular septum, and pulmonary stenosis of the typical tetralogy of Fallot with septal defect. Briefly, a word about the first group:

(Slide.) Description of these instruments has not been published, and it might be interesting to spend a minute describing them. We have what we call an expanding valvulotome, made so that the wound in the heart may be kept small. We have borrowed from the urologists the principle of a retreating or sheathe blade. The dilator is built on the same principle. Indicators on the instruments show how widely the valvulotome or dilator is open.

(Slide.) Here you see both instruments completely opened. This basket type of dilator is made so that when it is in the pulmonary artery completely expanded, blood can still flow through the vessel. This is seemingly rather important.

(Slide.) The operative approach is a left submammary incision. The closed valvulotome is thrust into the right ventricle. Then by palpation and observation of the pulmonary artery we determine how widely to open the valvulotome.

(Slide.) The valvulotome is thrust through the stenotic pulmonary valve, closed, and withdrawn. A finger is put over the opening momentarily and the dilator is then inserted. We use the dilator to complete the division of the stenotic valve as we do not dare cut to the very edge of the pulmonary artery. The dilator can be rather leisurely expanded as the pulmonary artery is observed, and blood can continue to flow through the vessel while this is being done. The opening in the heart is closed with two stitches.

To throw some light on the subject of pulmonary stenosis with a septal defect, we analyzed 24 post-mortem hearts of patients who had died of tetralogy of Fallot. It was interesting to find that we had exactly the same percentages that Dr. Blalock presented yesterday. In nineteen of the twenty-four there was infundibular stenosis of varying degree or atresia. In four, there was combined infundibular and valvular stenosis. In only one was there complete stenosis of the valve itself. In these five patients, incision, not excision, would have been a valuable procedure.

It is appropriate that we bow to the courageous young men, because what they are doing is an extremely valuable stimulus to further study. However, in view of the high mortality associated with reaming out the stenotic segment, I still feel that we should do the shunt operation until one can more safely go inside the heart.

DR. BAILEY (closing).—We did not attempt to present a pathologic paper, although such might have been very desirable. We did not have sufficient pathologic material to present anything comprehensive. We presented a technical and clinical paper on thirty practically consecutive cases. You will note, both from Dr. Blalock's statistics yesterday and from Dr. Potts' today, that we are apparently out of line with the findings in an autopsy series of cases of tetralogy of Fallot. However, Brock, in twenty-six similar living cases, found a distribution of types of pulmonic obstruction almost exactly the same as ours. Our point would be that this is a living series, the type of patient you are liable to meet to take to the operating table, whereas many of the other cases have probably died at an early age and, because of the extremes of pathologic variation, did not live to be considered for surgery. We also feel that part of the discrepancy may be based upon the fact that anatomic infundibular septum may be quite different from functional infundibular septum, in that probably many hearts which seem superficially normal actually have a residual or partial infundibular septum, which a pathologist would so classify if he were looking for it. They do not obstruct the flow of blood through the pulmonary artery and so are not of clinical significance.

We realize, of course, that there is a great difference between pure pulmonic stenosis and the tetralogy of Fallot. There is no question in anyone's mind, I think, that the case of pure pulmonic stenosis is usually valvular and can be treated very well by the methods which Mr. Brock, Dr. Blalock, and Dr. Potts have so well presented. There probably is also no great question when true valvular stenosis occurs in tetralogy of Fallot, because obviously the direct technique is then quite comparable and the results should be excellent. The only argument, I believe, is with regard to the type of surgery for the infundibular type. We too feel that there is a certain group of severe infundibular stenoses which will never be suitable for the direct approach. Our suggestion is that, having opened the pericardium, an incision be made in the heart and a finger, the little finger or the index finger according to the size of the heart, be passed into the right ventricle, which seems to tolerate it well. Then the exact pathology can be pretty well determined and one can immediately tell whether there is any hope of doing a direct resection of the obstructing infundibular septum. On a theoretic basis, as Dr. Blalock pointed out yesterday, and Dr. Glover today,

it would be better to diminish the number of defects by removing the pulmonary obstruction rather than increase the number by adding a patent ductus arteriosus. But that, of course, may not always be entirely practical.

I think Dr. Potts' instrument for cutting the pulmonary valve is superb, and we have already ordered one and hope to be able to use it some day. It is certainly superior to the instruments we have been using. I think the chief criticism of this paper is with regard to the present operative mortality and morbidity. We really lost seven patients, the last one several weeks postoperatively, because I inadvertently avulsed a pulmonary valve. But this presentation was of our first thirty cases. Without meaning any disrespect to the great men we have talked about, I believe Dr. Blalock's mortality in his first 144 cases was approximately the same as ours in this series, and so we hope to do better as we learn better.

TREATMENT OF CORONARY ARTERY INSUFFICIENCY BY IMPLANTATION OF THE INTERNAL MAMMARY ARTERY INTO THE LEFT VENTRICULAR MYOCARDIUM

ARTHUR VINEBERG, M.D.
MONTREAL, QUE.

IN THIS paper a preliminary report is given in human cases of coronary insufficiency which have been treated by implantation of the left internal mammary artery into the left ventricular myocardium. The experimental data upon which this procedure is based are briefly described.

Attempts to increase the circulation of the myocardium in cases of coronary artery insufficiency may be grouped as follows: (a) Vascularization through the surface of the heart by grafts and granulomas.[1-3] (b) Cardiac vein ligation.[4] (c) Arterialization of the coronary venous system.[5]

A different approach to the vascularization of the ventricular myocardium was first attempted by us in 1945.[6] The left internal mammary artery was employed as a source of fresh arterial blood for the ventricular myocardium. The internal mammary artery was transected and detached from its chest wall bed. It was then placed within a tunnel in the ventricular myocardium. An anastomosis developed between the implanted internal mammary artery and the left coronary circulation. The presence of the anastomosis was proved by injection studies, radiographs, plastic casts, and serial sections. (Figs. 1, 2, 3*A*, 3*B*, 4).

In our early experiments, approximately 60 per cent of implanted internal mammary arteries failed to form an anastomosis.[7] Experiments were conducted in an effort to discover some of the factors which were responsible for the anastomosis. It was found that an anastomosis between the implanted internal mammary artery and left coronary vessels occurred with greatest frequency when (1) A short length of artery is freed from the chest wall. (2) The internal mammary artery is placed in the inner two-thirds of the myocardium. (3) The sixth intercostal is left open when buried within the myocardium.

It is important to avoid trauma and infection which favor thrombosis. Thrombosis limits the size of the anastomosis. Small anastomoses, however, frequently develop through a recanalized thrombus.

Anastomoses occurred in from 50 to 75 per cent of the animals, dependent on the technique of implantation used. The next step was to determine the value of such an anastomosis in affording protection against coronary artery occlusion. This was gauged by a study of the mortality rate and the development of ventricular infarcts following ligation of the anterior descending branch of the left coronary artery.

From The Department of Surgery, Royal Victoria Hospital, and the Department of Experimental Surgery, McGill University.

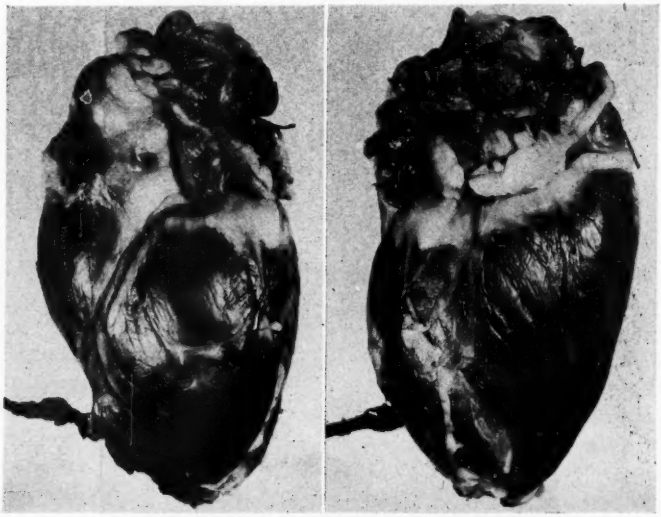
Read at the Thirty-first Annual Meeting of The American Association for Thoracic Surgery at Atlantic City, New Jersey, April 16-18, 1951.

In a series of twenty-six animals divided into four groups, the average survival rate after anterior descending branch ligation was 50 per cent. In one group it was 75 per cent. Sixty-nine per cent of the animals surviving did so without infarction. The surviving animals all showed an extensive mam-

Fig. 1.—Roentgenogram of the left coronary tree, which has been filled by injecting the left internal mammary artery seventeen weeks after it was implanted into the left ventricular wall.

Fig. 2.—Roentgenogram shows heart of animal (162) with injection mass filling the anterior descending and circumflex branches of the left coronary artery fourteen weeks after implantation. This animal survived anterior descending branch ligation.

mary-coronary anastomosis. In one-third, the anastomosis was established through a recanalized thrombus within the internal mammary artery. In no single case has an animal died or developed infarction following anterior descending branch ligation when a large anastomosis existed.



A. *B.*

Figs. 3,*A* and 3,*B*.—The heart of animal (39) with blue Schlesinger's solution filling the branches of the coronary artery. The injection was introduced through a 13-week-old internal mammary artery implantation.

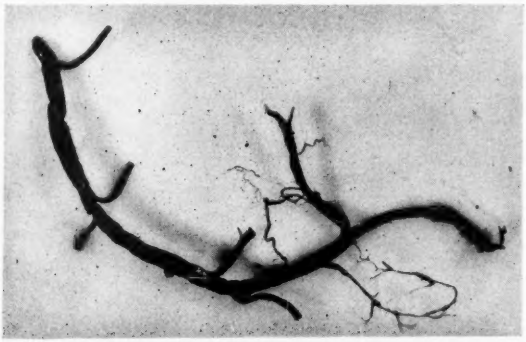


Fig. 4.—Shows a cast which has been made by injecting the internal mammary artery with a plastic substance forty-six weeks after implantation into the left ventricular wall. The small sharply cut off branches to the right are intercostals tied with cotton. The fine arborizations to the left have developed within the heart muscle.

In a control group of animals without internal mammary implantation, death occurred in 90 per cent, and a 5 by 5 cm. infarction developed in the surviving 10 per cent.[8, 9] The facts seemed to indicate that an implanted in-

ternal mammary artery is capable of carrying on the circulation of the left ventricle after coronary occlusion. The evidence, however, was largely statistical, thus further proof was sought.

DIRECTION OF BLOOD FLOW IN INTERNAL MAMMARY ARTERY

The direction of blood flow through the implanted internal mammary artery was studied in order to determine whether it was bringing blood to the ventricular myocardium. Direct determination of blood flow in the internal mammary artery was difficult, so the indirect method was used. Animals which survived anterior descending branch ligation of the left coronary artery were

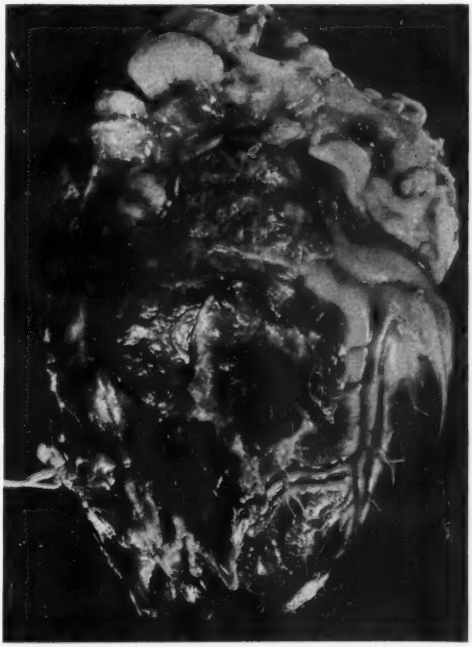


Fig. 5.—Heart of animal No. 10, M. series; this animal underwent anterior descending branch ligation sixty-seven days after internal mammary implantation and survived. The implanted internal mammary artery was ligated thirty-seven days later and the animal died of a large anterior wall left ventricular infarct.

subjected after four weeks to complete and sudden occlusion of the implanted internal mammary artery. If the internal mammary artery was maintaining the circulation of the left ventricle, then following its ligation, either death or infarction should result. This is exactly what happened. In three animals with an internal mammary implant which had survived anterior descending branch ligation, the internal mammary artery was ligated. One animal died within twenty-four hours, and displayed an edematous cyanotic area of the anterior wall of the left ventricle. One survived for three days before dying

from a large infarct in the same location (Fig. 5). The third animal survived, but examination of the sacrificed specimen revealed that multiple intercoronary anastomoses were present.

Following these experiments, there seemed little doubt as to the formation and value of a coronary mammary anastomosis. However, skepticism was expressed with regard to the character of the anastomoses and to their duration.

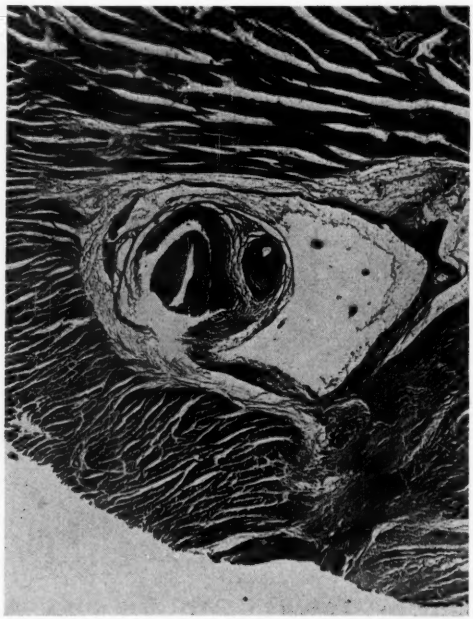


Fig. 6.—Represents a serial section of an implant lying within the muscle of the myocardium fifty-eight weeks after implantation. Note the branch lying alongside of parent vessel. This branch has been traced into the myocardium.

DURATION OF ANASTOMOSIS

Recently, Glenn and Beal[10] confirmed the development of an anastomosis between an implanted internal mammary artery and the coronary vessels. However, they stated that the new vessels tend to disappear at the end of eight weeks. They further suggested that the new vessels were small and resembled granulation tissue.

In our series, the average interval from implant to sacrifice was eleven weeks (Table I). Some animals were kept fifty-eight weeks after implantation. The anastomoses at the end of that time not only persisted, but were large enough to protect against death and infarction following ligation of the anterior descending branch.

The anastomoses which developed have been shown by serial sections, special muscle and elastic stain studies, and by casts to be formed by true arterial branches of the implanted internal mammary artery (Figs. 6, 7, 8, 9).

The experimental results just described were obtained by implanting the internal mammary artery into normal dogs' hearts. It was suggested that in human coronary insufficiency such a procedure would be of little value because of the presence of occluded coronary vessels and associated myocardial ischemia. It was, therefore, decided to produce coronary artery insufficiency experimentally in the dog.[11] This was done by wrapping the origin of the anterior descending branch of the left coronary artery with a sclerosing type of cellophane. The

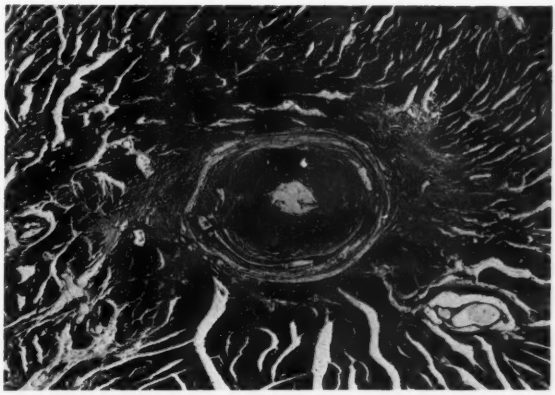


Fig. 7.—Dog 7. Internal mammary artery one hundred twenty-two days after implantation shows artery lying between heart muscle fibres with many branches. There is very little reaction around the implant and the scar tissue appears inactive. Note branch at 7 o'clock.

TABLE I. DURATION OF ANASTOMOSIS.

TYPE OF ANASTOMOSIS	NO. OF ANIMALS	PRESENCE OF ANASTOMOSIS AFTER IMPLANT (WEEKS)	VALUE OF ANASTOMOSIS AFTER LIGATION OF ANT. DESC. BRANCH LT. CORONARY ARTERY
Microscopic:	1	5	Protection against death or infarction afforded in 3 animals only.
	1	6	
Anastomosis small due to thickened or partially thrombosed internal mammary artery.	1	7	
	2	8	
	2	11	
	2	12	
	2	13	
	1	14	
	12		
Macroscopic:	1	6	No deaths or infarction occurred.
	2	7	
Anastomosis large, internal mammary artery patent.	5	9	
	5	11	In cellophane coronary artery sclerosis marked improvement in exercise tolerance occurred.
	4	12	
	2	14	
	1	17	
	1	18	
	3	19	
	1	21	
	1	31	
	1	41	
	1	46	
	1	58	
	29		

cellophane surrounding the origin of the anterior descending branch of the left coronary artery set up a periarterial fibroplasia which resulted in a gradual contraction through scar tissue of the coronary artery and narrowing of its lumen. This caused a reduction in blood flow through the narrowed vessel and resulted in ischemia of the left ventricular muscle supplied by the anterior descending branch of the left coronary artery. The degree of myocardial ischemia was evaluated by estimating the exercise tolerance of the animal on a motorized treadmill. Before the cellophane wrap was placed around the coronary artery, the animals would run nine to twelve minutes at 8½ miles per hour on the treadmill before becoming extremely anxious, begin to whine, and salivate prolag on the mill, and would break alternatively from a gallop to a run. Eventually they would become anxious to escape the mill. When the exercise was discontinued, these animals would pant, but would drink water and appear

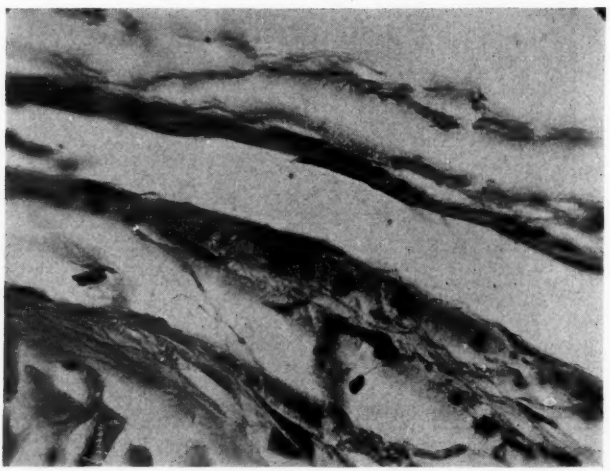


Fig. 8.—High-power view of small branch showing well-developed muscle and elastic tissue in same animal as shown in previous slide at 7 o'clock.

similar to any other normal dog after exercise. Five months after these animals had had a piece of cellophane wrapped around their anterior descending branch of the left coronary artery, they could run for one and six-tenths minutes on the treadmill before becoming extremely anxious, begin to whine, and salivate profusely. If the exercise was not terminated, they would attempt to lie down or drag their feet on the revolving platform. When the mill was stopped, they would drop where they stood and resist all coaxing to move for some minutes and would not drink water. Animals that had reached this stage were then subjected to a left internal mammary artery implant. Four months after the implant those animals which had definitely developed an internal mammary coronary anastomosis had a return of exercise tolerance to seven minutes or more. This occurred in spite of a completely occluded anterior descending branch of the left coronary artery. When an internal mammary coronary anas-

tomosis failed to develop, there was no improvement in exercise tolerance in such animals after implantation. Because of these experimental results it was thought that implantation of the internal mammary artery into the left ventricular myocardium might be of value in the treatment of human cases of coronary artery insufficiency.

HUMAN CASES OF CORONARY ARTERY INSUFFICIENCY TREATED BY INTERNAL MAMMARY ARTERY TRANSPLANT

Selection of Cases.—The estimation of clinical results is always difficult and the results of any given surgical procedure may vary according to the severity of the disease process at the time of operation. There are certain well-known pathologic facts concerning coronary artery sclerosis and thrombosis which greatly influence the selection of cases for internal mammary artery implant.

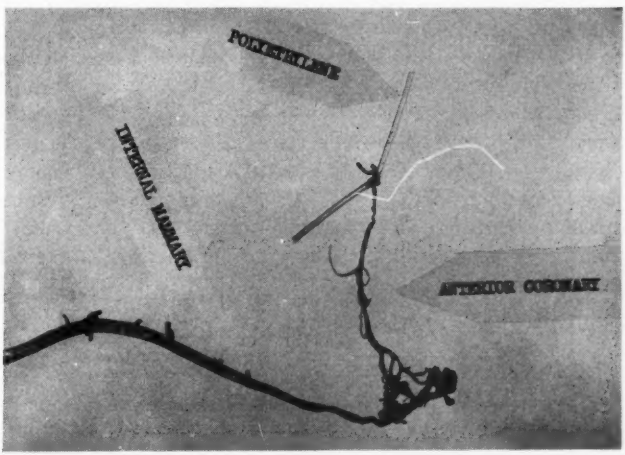


Fig. 9.—Shows a cast made by injecting the implanted internal mammary artery twenty-two weeks after implantation. Note the new branches of the implanted internal mammary artery which join with those of the anterior descending branch of the left coronary artery. A piece of polyethylene tubing was tied around the anterior descending branch at its origin before digestion was started.

Perhaps the most important is the fact that coronary artery sclerosis in general is confined to the first 3 or 4 cm. of the coronary arteries. It has been stated that the arteries distal to the first 3 or 4 cm. of the coronary vessels show lesser degrees of sclerosis and rarely is sclerosis seen after the 3rd or 4th order of branching.[12, 13] It has been shown that in cases of severe coronary artery sclerosis, the vessels lying within the heart muscle are generally free of arterial disease. Thus, an internal mammary artery placed between ventricular muscle fibers is in an area where the arteries are comparatively healthy. In this way, fresh blood can be brought to the network of nonsclerosed arteries which exist beyond the points of coronary artery obstructions.

In cases of coronary artery thrombosis with myocardial infarct, the picture is entirely different. In these cases, if the patient survives, an area of myocardial muscle undergoes degeneration and eventually heals by scar formation;

and there should be healthy muscle surrounding the area of the healed infarct. It is also stated that during the process of healing new blood vessels grow into the infarcted area. Thus, the history of a left coronary artery thrombosis with recovery does not constitute a contraindication to internal mammary implantation. The new living artery can be placed in healthy muscle which is present at the edge of the healed infarct and, if necessary, into the intraventricular septum itself. With this in mind, it is clear that the patients who have recovered from coronary artery thrombosis and infarction may be considered as candidates for an internal mammary artery transplant. One of our patients was known to have had two attacks of coronary artery thrombosis with posterior infarction. At operation there was still what appeared to be good muscle posteriorly. There was, however, evidence of scarring on the posterior surface towards the apex which scarring extended for half an inch or more on the anterior surface of the left ventricle. The internal mammary artery was placed into healthy muscle just proximal to this scarred area. We have been reluctant to operate upon patients who are able to carry on their normal daily activities. We have, to date, operated only upon those patients who are unable to carry on because of the severity of their anginal pain. Patients with an enlarged left ventricle and myocardial decompensation have been considered poor risks, and have not been accepted. Every attempt has been made to exclude other sources of anginal pain, and to make certain that the pain from which the patient is suffering is due to coronary insufficiency. Where there is a doubt, and particularly when other organic disease such as cholelithisis exists, the associated disease has been treated first.

CLINICAL RESULTS

We have operated on four human cases suffering from coronary insufficiency.

CASE 1.—The patient, aged 53 years, was admitted to Royal Victoria Hospital on April 24, 1950. He had been unable to work for three years because of substernal pain which radiated to the left jaw and down the left arm to the wrist, and was present day and night. It was first noticed fourteen years prior to admission, gradually becoming more severe. Some, but not complete, relief was obtained by nitroglycerine. Exercise tolerance was limited to one city block; he walked very slowly before onset of anginal pain occurred. There was a history of 40 pounds loss of weight in the past ten years. There was also a history of intolerance to fatty foods with eructations of gas and inability to eat a large meal.

All investigations were negative, except for the electrocardiograms which showed marked coronary insufficiency, accentuated by slightest effort. This was a case of angina status.

On April 28, 1950, the left internal mammary artery was implanted into the left ventricular myocardium. This was carried out through a left transthoracic approach and the sixth intercostal artery was cut and was pulled with the internal mammary artery into a tunnel in the myocardium. Except for a continuously low blood pressure throughout the operation, the patient appeared to tolerate the operation very well. The postoperative convalescence was uneventful until sixty hours after operation, at which time he developed sudden severe substernal pain and died two hours later. The interval between completion of operation and death was approximately sixty-two hours.

Pathologic Findings at autopsy revealed that the three main coronary arteries were pipe stem in character. The right coronary artery was completely blocked by an old, firm grayish thrombosis. The left anterior descending branch was completely occluded for a distance of 1 cm. by a recent, soft, dark-brown thrombosis. The internal mammary artery was

patent throughout (Fig. 10). There was no hematoma at the site of implant. Death was due to a recent thrombosis of the anterior descending branch of the left coronary artery with ventricular infarction. It is our opinion that had this man's blood pressure been maintained throughout the operation and not been permitted to drop to as low as 70/60, which it was at the time of implantation, that this patient might not have developed a fresh coronary artery thrombosis. The maintenance of blood pressure is particularly important in cases of coronary artery disease. Slowing of the rate of blood flow through a narrowed irregular coronary artery will favor thrombosis.

In our last three patients, blood pressure has been maintained by means of a continuous drip of neosynephrin, which is started at the same time as the anesthetic. In these patients the blood pressure was well maintained throughout the operation. All three patients have had a comparatively uneventful postoperative recovery.

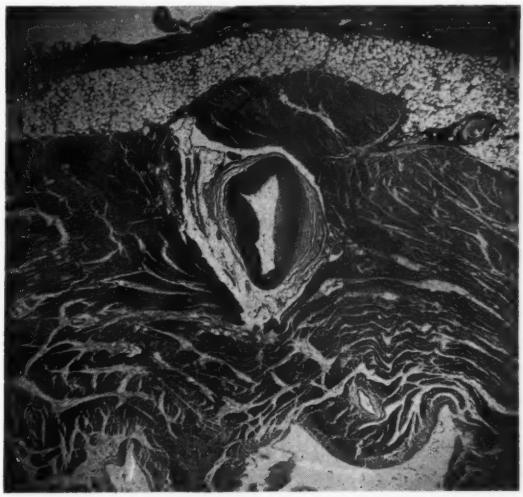


Fig. 10.—Internal Mammary Artery of Case No. 16415; Sixty-two hours after implantation lying within the myocardium. The arterial lumen is free of thrombus. There is little reaction around the artery and there is no hematoma. Note preservation of surrounding myocardial muscle fibers.

CASE 2.—The patient was a man 54 years of age who suffered from severe precardial pains which radiated down the left arm, and inability to ingest solids. This pain was brought on by emotion, exercise, or the ingestion of solid food, and prior to operation this patient had lived on a liquid diet for three months and had not worked for nine months. There was dyspnea on slight exertion. Exercise tolerance was limited to half a city block. Electrocardiograms showed coronary artery insufficiency accentuated by exercise; all other investigations were negative. On November 2, 1950, his left internal mammary artery was implanted into the left myocardium. His postoperative course, except for abdominal distention, was uneventful.

The patient left the hospital and flew to his home in the Canadian West at the end of five weeks, and at the present time is free of pain, is working a full day, and able to take solid food without pain.

CASE 3.—The third patient, a man 49 years of age, suffered from severe angina pain for four years. The pain started in the substernal region and radiated down the left arm. Occasionally the pain went to the throat and jaw. The pain was made worse by any change in pace, by exercise, or by emotion. Electrocardiograms showed evidence of an old healed posterior wall infarct. He was operated on Nov. 20, 1950. At operation the posterolateral

LIBRARY
BOSTON UNIVERSITY
SCHOOL OF MEDICINE

wall, the apex, and half an inch of the anterior wall of the left ventricle were found to be scarred. The internal mammary artery was implanted into healthy muscle proximal to the apical scar. Except for a paralytic ileus, which was easily controlled, the patient's postoperative convalescence was uneventful. He returned to his home at the end of four weeks and was free of pain until Jan. 2, 1951, when he developed pain in the left wrist and forearm. This pain was associated with exercise or emotion. There was no pain in the pectoral region and none in the throat. Electrocardiograms taken in March, 1951, showed continued improvement. His present pain is interpreted as that which sometimes occurs after an anterior wall infarction, and has been compared to the shoulder arm syndrome.

CASE 4.—This man, aged 55 years, suffered from substernal pain for two years which radiated from midsternum down both arms. Pain was brought on by exercise, emotion, and a moderately fair-sized meal. His preoperative electrocardiograms suggested the presence of an old healed anterior wall infarction. His exercise tolerance was poor. On March 1, 1951, he was operated on. A large healed infarct was found on the anterior wall of the left ventricle. The internal mammary artery was implanted into healthy muscle, lateral to the scarred area. The postoperative convalescence has been uneventful.

Abdominal distention which occurred in Cases 2 and 3 seemed to be avoided by early prophylactic decompression of the stomach with Wagensteen suction. The patient returned to his home in Nova Scotia four weeks after operation at which time he was free of pain.

DISCUSSION

In our experimental work it has been shown that when the internal mammary artery is placed in the ventricular myocardium, it forms new arterial branches which anastomose with the left coronary circulation. When this occurs, the heart is protected against death by infarction following the occlusion of the anterior descending branch of the left coronary artery. It has also been shown that those animals which have survived ligation of the anterior descending branch of the left coronary artery, die or develop infarction when the implanted internal mammary artery is occluded. An internal mammary coronary artery anastomosis has been shown to be of functional value. It has relieved artificially produced coronary artery insufficiency. We would like to point out that the implant procedure is different from other grafting operations. The internal mammary artery is not placed on the surface of the heart but is pulled into position by blunt dissection between the heart muscle fibres. Little damage is done to the heart muscle fibres and practically no reaction occurs around the implanted artery. Branches from the implant reach the deep coronary arteriolar plexus.

It is reasonable to assume on the basis of our experimental work and the pathological facts of coronary artery sclerosis that an internal mammary artery implant may be of value in the treatment of human coronary artery insufficiency. Cases have to be carefully selected and treated by a medical-surgical team, and it is our opinion that the use of quinidine pre- and postoperatively with procaine during the operation is important in preventing ventricular fibrillation. Our first patient, we believe, developed his coronary thrombosis because of the continuous low blood pressure which was present throughout the operation. In order to bring these patients through an intrathoracic operation without further damaging their coronary artery system, we believe that it is necessary to maintain their blood pressures throughout the entire operative procedure. The postoperative care of these cases is fundamentally a medical problem. Unlike other

thoracic cases, these patients should not be moved frequently in the first few postoperative days. It would seem best to treat them postoperatively much in the same manner as a case of coronary artery thrombosis. Interpretation of postoperative electrocardiographs is difficult because of the disturbances created by the implantation of a pulsating artery into the anterior wall of the left myocardium. Clinically there has been no evidence of coronary artery thrombosis developing after operation in the three cases which have survived.

It is too early to estimate results other than to say that the patient in Case 2 has returned to work and is free of pain. It is now five months since his operation. We believe the operation should have a very low mortality rate. The actual work on the heart takes about two and one-half minutes, and causes the heart no embarrassment. Should the implant fail to form an anastomosis, the patient should be no worse off than before operation.

SUMMARY

1. The internal mammary artery has been shown experimentally to be capable after implantation of carrying the circulation of the left ventricle.

2. The internal mammary artery has been successfully transplanted into the ventricular myocardium in man. The operative procedure is simple and appears to cause no disturbance to cardiac function.

3. The implanted artery, when it forms an anastomosis, furnishes a third artery to the left ventricle beyond the points of coronary artery occlusion.

4. The internal mammary artery in man, as in the animal, was found to be completely patent sixty-two hours after implantation in the one fatality that occurred.

5. Three of four patients have survived the operation. One is well and working at the end of five months, and the others show improvement. There is no evidence that the procedure causes any harm to the existing coronary circulation.

I wish to express my appreciation for the counsel, criticism, and continued support which have been given by Dr. Gavin Miller, Dr. Lyman Duff, Dr. Donald Webster, and Dr. C. A. MacIntosh. In particular do I wish to thank Dr. G. R. Brow for his careful selection of cases for operation and for his help in their postoperative care.

REFERENCES

1. Beck, C. S., and Tichy, V. L.: The Production of a Collateral Circulation to the Heart, Am. Heart J. **10**: 849, 1935.
2. O'Shaughnessy, L.: An Experimental Method of Providing a Collateral Circulation to the Heart, Brit. J. Surg. **23**: 665-670, 1936.
3. Beck, C. S.: The Development of a New Blood Supply to the Heart by Operation, Ann. Surg. **102**: 801-813, 1935.
4. Fauteux, M.: Experimental Study of the Surgical Treatment of Coronary Disease, Surg. Gynec. & Obst. **71**: 151, 1940.
5. Beck, C. S., Stanton, E., Batiuchok, W., and Leiter, E.: Revascularization of Heart by Graft of Systemic Artery into Coronary Sinus, J. A. M. A. **137**: 436-442, 1948.
6. Vineberg, A. M.: Development of Anastomoses Between Coronary Vessels and Transplanted Internal Mammary Artery, Canad. M. A. J. **55**: 117, 1946.
7. Vineberg, A. M., and Jewett, B. L.: Development of an Anastomosis Between the Coronary Vessels and a Transplanted Internal Mammary Artery, Canad. M. A. J. **56**: 609, 1947.

8. Vineberg, A. M.: Development of an Anastomosis Between Coronary Vessels and Transplanted Internal Mammary Artery, J. THORACIC SURG. **6**: 839, 1949.
9. Vineberg, A. M., and Niloff, P. H.: The Value of Surgical Treatment of Coronary Artery Occlusion by Implantation of the Internal Mammary Artery into the Ventricular Myocardium, Surg. Gynec. & Obst. **91**: 551-561, 1950.
10. Glenn, F., and Beal, John M.: Fate of an Arterial Implant in the Myocardium, Surgery **27**: 841-847, 1950.
11. Vineberg, A. M., Niloff, P. H., and Miller, D.: Treatment of Coronary Artery Insufficiency by Implantation of the Internal Mammary Artery into the Left Ventricular Myocardium, Proc. Roy. Coll. Physicians and Surgeons, Canada, Montreal, December, 1950. In press.
12. Blumgart, H. L., Schlesinger, M. J., and Davis, D.: Studies in the Relation of the Clinical Manifestations of Angina Pectoris, Coronary Thrombosis and Myocardial Infarction to Pathological Findings, Am. Heart J. **19**: 1-91, 1940.
13. Blumgart, H. L., Schlesinger, M. J., and Zall, P. M.: Angina Pectoris, Coronary Failure and Acute Myocardial Infarction, J. A. M. A. **116**: 91-97, 1941.

DISCUSSION

DR. SAMUEL A. THOMPSON, New York.—Dr. Vineberg has shown by his experiments that anastomosis between the internal mammary and the coronary blood vessels can be accomplished, and in this way additional vascularization of the myocardium occurs. We have approached the problem of coronary insufficiency in a different manner. We perform cardiopexy by instilling powdered magnesium silicate inside the pericardial sac. This produces a granuloma and causes additional vascularization by extracardiac anastomosis as well as by intercoronary anastomosis. The myocardium is converted from an ischemic condition to one of hyperemia. We have operated upon fifty-two patients, the first one is now thirteen years after operation, and we do not feel that there is any tendency for constrictive pericarditis to develop following this procedure.

I would like to emphasize that this type of treatment is not a cure for coronary disease. It is a method of rehabilitating a group of cardiac cripples. Our operative mortality and hospital mortality has been 12 per cent. Of the surviving patients followed to the present time, or to the time of their death, 85 per cent have been more than 50 per cent improved and rehabilitated. Seventy per cent of them are more than 66 per cent improved, and 20 per cent of them claim that they are completely normal.

I would like to ask Dr. Vineberg if he feels that his method gives vascularization beyond the local area in which the blood vessel is grafted.

DR. VINEBERG (closing).—Yes, Dr. Thompson, I believe that the implanted internal mammary artery is capable of taking over the circulation of the entire left ventricle. We have no evidence that it vascularizes the right ventricle.

Approximately 50 per cent of all cases of coronary artery thromboses involve the left coronary artery and it is in these cases that there is the highest mortality and morbidity. The internal mammary artery implant experimentally forms an anastomosis with the left coronary circulation on an average of 50 per cent. In some series, however, anastomosis has occurred in 100 per cent of the implants. When the anastomosis does form it completely revascularizes the left ventricle, and gives 100 per cent protection against death and infarction, following occlusion of the anterior descending branch of the left coronary artery.

CONGENITAL CYSTIC DISEASE OF LUNG ASSOCIATED WITH ANOMALOUS ARTERIES

FREDERICK G. KERGIN, M.D., M.S., F.R.C.S.
TORONTO, ONT.

IN 1946 Pryce published the first comprehensive description of a congenital lesion of the lung which has two components, a maldevelopment of part of the bronchial tree to a lower lobe with an associated distribution of arterial blood to the affected portion of the lung by way of an anomalous artery arising from the aorta. In 1947, he, with Sellors and Blair, published a second paper dealing further with the etiological, pathologic, and clinical aspects of the condition. Both papers were based on a study of pathologic material obtained from seven patients who had been treated for this condition by pulmonary lobectomy.

The bronchial abnormality may affect either lower lobe, more commonly the left, and involves the posteromedial portion of the lobe. In this area the bronchial maldevelopment may be of the nature of bronchiectasis of a congenital type or, more commonly, there is a bronchopulmonary mass made of cysts of bronchial origin surrounded by nonfunctioning lung tissue of a primitive type. In some cases the congenital separation of this mass from the bronchial tree appeared to be complete, while in others there seemed to be continuity of developmental origin. In some a secondary connection with the bronchus appeared to have occurred as the result of infection. The symptoms which brought these patients to treatment were due to infection of the bronchopulmonary mass. In those cases which had a pre-existing bronchial connection this could occur by bronchial spread, but in others in which the separation had been complete it was necessary to postulate direct spread of infection from contiguous lung, or hematogenous infection.

In the examples studied by Pryce there was a failure of development of branches of the pulmonary artery to the affected part of the lobe. Instead of venous blood, carried by the pulmonary artery, the bronchopulmonary mass was supplied with arterial blood through an anomalous artery of considerable size arising from the aorta and passing to the lower lobe between the leaves of the pulmonary ligament. This artery may arise either from the lower thoracic aorta or from the abdominal aorta and then pass upward through the diaphragm to enter the ligament. Pryce stated that after passing through branches ramifying over the mass this blood then drains into branches of the inferior pulmonary vein. He pointed out that, although this artery carries oxygenated blood at systemic blood pressure, it has the histologic structure of a pulmonary artery, and is subject to early atheromatous degeneration.

Read (by title) at the Thirty-first Annual Meeting of The American Association for Thoracic Surgery, Atlantic City, New Jersey, April 16-18, 1951.

Pryce is impressed by the fact that systemic arteries of this type are sometimes found supplying normally connected and developed lung, and from this and other considerations concluded that the vascular anomaly is primary. He postulated that in the course of development of a lung, the bulbous tip of one branch of the primitive bronchus may come into relationship with and be "captured" by part of the dorsal capillary plexus, which drains into the primitive dorsal aorta. With further development the connection may persist, giving rise to an anomalous artery or arteries arising from the aorta and supplying lung. If this abnormal connection does not lead to a distortion of growth of the affected bronchus, the result is an anomalous artery supplying otherwise normal lung. If, however, the traction resulting from the abnormal connection results in dislocation of the bronchus, some form of congenital bronchial lesion results, again with anomalous arterial connection. If the abnormal mass remains within the lung, the condition under discussion results, which Pryce has called "intralobar sequestration." If the dislocation is more complete, the abnormal lung mass becomes separated from the lobe to form a lower accessory lung, which he has termed "extralobar sequestration." Finally, he suggests that there may be death of the captured bulbous tip, and this results in agenesis of part or all of the affected lung.

Pryce's theory seems to explain the known facts in regard to anomalous vessels connected to lung better than any other, and has the virtue of relating intra- and extralobar sequestration to each other as being differences of degree rather than kind. Case 5, to be described below, is an example of both intra- and extralobar sequestration in relation to the same lower lobe, which lends some support to the theory. This anomaly apparently has not been described before.

In 1950 Bruwer, Clagett, and McDonald of the Mayo Clinic reported five cases. They expressed agreement with Pryce's views in regard to the embryological error responsible for the anomaly. In their review of the literature they had found reports of twenty-six similar cases, and mentioned that in three of these there had been a fatality because of hemorrhage from the anomalous vessel.

The present report is based on five examples of this condition which have been encountered at the Toronto General Hospital. In the earlier records there are three other cases of localized congenital cystic disease of the lower lobe which seem to represent examples of the same condition, but as there is no clear cut description of the anomalous artery, they are excluded from the series.

CASE REPORTS

CASE 1.—J. S., a man, aged 17 years, was admitted on Sept. 17, 1941. He was perfectly well until six months before admission, when he developed pneumonia. He continued to have a cough, dry at first and later productive of a small amount of mucoid sputum. On one occasion he had a small hemoptysis of bright blood. Examination showed slight diminution in lung resonance and diminished breath sounds at the left base.

Roentgenograms (Fig. 1) demonstrated three ovoid cystic spaces in the left lower lobe, situated posteriorly. One of them showed a fluid level. A diagnosis of cystic disease of the lower lobe was made.

At operation (by Dr. R. M. Janes) there were no pleural adhesions. There was no pulmonary ligament of the usual type, the lung was directly applied to the aorta and esophagus. An artery 6 mm. in diameter passed directly forward from the aorta into the lower portion of the lower lobe. Dissection lobectomy was done.

Examination of the lobe showed that the postero-medial portion contained a firm, rubbery mass, in which individual rounded cysts could be felt. This part of the lung was yellow-pink in color, and devoid of pigment. On cutting the lobe the cysts were filled with inspissated mucus, except one which had drained into the lower lobe bronchus. The cysts were lined by typical bronchial epithelium.

The patient made a good recovery from the operation and has remained perfectly well.

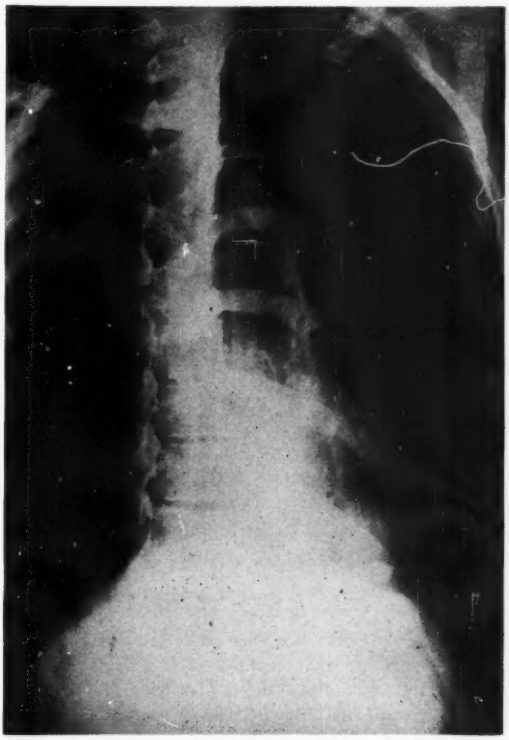


Fig. 1.—Case 1. Oblique view to show rounded density behind heart. In the original film a faint fluid level is visible close to vertebrae.

CASE 2.—H. Z., a woman, aged 19 years, was admitted to the hospital on Oct. 12, 1948, with a history of pneumonia on the left side at the ages of 10, 12, and 15 years, and again in January, 1948. At the age of 10 years the left chest had been drained by a tube for a few weeks. Since the pneumonia in 1948 she had had two ounces of green sputum per day. Examination showed diminished breath sounds at the left base posteriorly and the scar of the previous drainage.

Roentgenograms (Fig. 2) demonstrated a large cystic area in the left lower lobe posteriorly, with two fluid levels. A diagnosis of infected bronchogenic cyst was made.

At operation the pleural space was obliterated. On freeing the lower lobe it was found that the posteromedial aspect was light pink in color with no deposition of pigment. The cyst almost filled the lobe. Passing up through the diaphragm and reaching the lobe via the inferior ligament was an artery 5 mm. in diameter. Dissection lobectomy was done.

Examination of the specimen showed that there was no distribution of the pulmonary artery to the involved area, but that the anomalous vessel connected with and drained into the pulmonary vein. There was a very small communication with the lower lobe bronchus, which appeared to be secondary. The cyst was lined by ciliated columnar epithelium.

The patient developed a postoperative empyema which cleared with drainage. When seen five months after operation she was perfectly well.

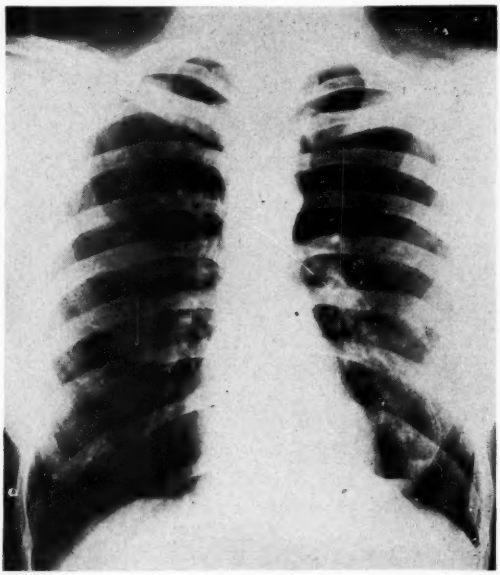


Fig. 2.—Case 2. Large cyst at left base with two fluid levels.

CASE 3.—W. O., a man, aged 60 years, was admitted to the hospital on Aug. 14, 1949. He first developed a dry cough five years before. For about three years he had brought up small amounts of mucoid sputum, often tinged with brown. For two months he had had repeated violent coughing attacks, and for two weeks had expectorated small amounts of dark blood after these attacks. General health was good, and there was no weight loss. There were no abnormal signs on examination.

Roentgenograms (Fig. 3) showed an irregular area of density at the right base, close to the mediastinum extending downward below the dome of the diaphragm. In both the posteroanterior and lateral views a fluid level was visible near the upper part of the density.

In this case the diagnosis of intralobar sequestration was considered, but seemed unlikely because of the age of onset of the symptoms. Bronchoscopic examination and examinations of sputum were negative for evidence of carcinoma; chronic lung abscess was considered the most likely diagnosis.

At operation on August 24, the lower lobe showed no adherence, except to the diaphragm. The posteromedial portion of the lobe was made up of a slightly irregular mass which was

pale pink in color, devoid of anthracotic pigment, firm and rubbery below, cystic above. On opening the inferior ligament a leash of vessels was found passing to this mass, and consisted of two arteries passing directly forward from the thoracic aorta, each 3 mm. in diameter, and a vein of similar size connected with the azygos vein. These vessels were tied and divided and the lobe removed by dissection lobectomy.

Examination of the specimen showed that the upper portion consisted of a cyst communicating with the lower lobe bronchus by a very small opening and lined by epithelium of a bronchial type. The lower portion contained many smaller cysts filled with mucus.

The patient made an excellent recovery. When seen two months later he had no complaints, and had noticed a decided improvement in his exercise tolerance since operation.

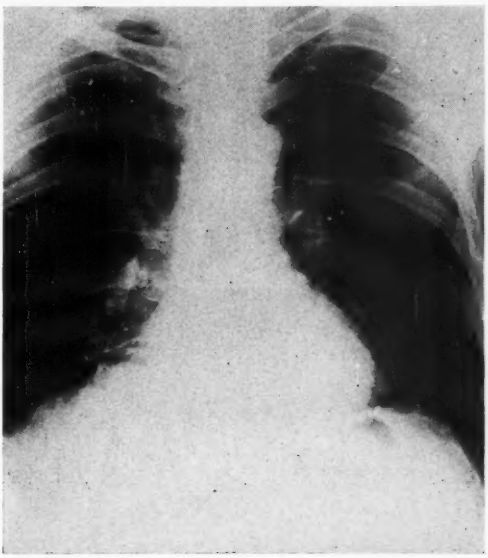


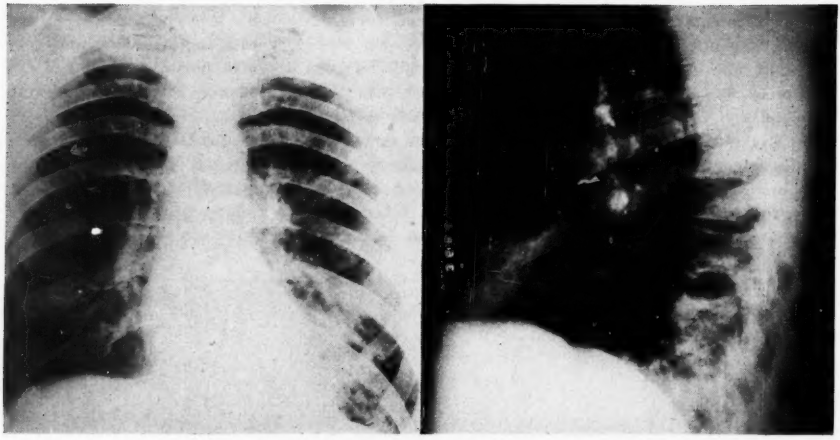
Fig. 3.—Case 3. Rounded density with fluid level close to heart at right base.

CASE 4.—P. K., a man, aged 34 years, was admitted to the hospital on Jan. 9, 1950. He complained of chronic cough with sputum for ten years. He had left-sided pneumonia in 1942 and 1946. There had been a gradual increase in the amount of sputum up to 4 ounces per day; for one and one-half years it had been foul, and it was noted that lying on the right side caused coughing. There was a moderate hemoptysis in 1948. There was moderate loss of energy and shortness of breath on exertion. Investigation at a sanatorium before transfer to the Toronto General Hospital had been negative for tuberculosis. Examination showed dullness, bronchial breathing, and coarse râles at the left base.

Roentgenograms (Fig. 4) showed an area of density in the posteromedial aspect of the left lower lobe. The upper portion consisted of a cavity 3 cm. in diameter with a fluid level, and below this were multiple rounded translucent areas about 1 cm. in diameter.

On the basis of the history, physical and radiographic findings a diagnosis of intralobar sequestration of the left lower lobe was made.

At operation there were no adhesions. The posterior portion of the lower lobe was yellow-pink in color, devoid of pigmentation, cystic in the upper portion, and rubbery below. An artery 6 mm. in diameter passed upward through the diaphragm, between the leaves of the pulmonary ligament, and entered the mass. After dividing this vessel a dissection lobectomy was done.



A. *B.*

Fig. 4,*A*.—Case 4. Posteroanterior view shows rounded area at left base with fluid level.
Fig. 4,*B*.—Case 4. Lateral view demonstrating cyst with fluid level above, and multiple rounded translucent areas below.

Fig. 5.—Case 4. Roentgenogram of lower lobe after bronchus, pulmonary artery, and anomalous vessel had been injected with plastic. Note translucent areas in lower part of specimen indicating mucus-containing cysts, not communicating with bronchus.

In the laboratory it was found that saline injected into the anomalous artery drained freely from the pulmonary vein. Plastic of different colors was injected into the bronchial tree, the pulmonary artery and the anomalous artery, and then after roentgenograms of the specimen were made (Fig. 5) the lobe was macerated to leave a plastic cast of these structures (Fig. 6). This demonstrated the size and distribution of the anomalous vessel, and also that the pulmonary artery did not distribute branches to the cystic mass. The lower,

Fig. 6.—Case 4. Cast obtained after maceration of specimen. Large anomalous artery below on right, distributed only to cystic portion of lobe.

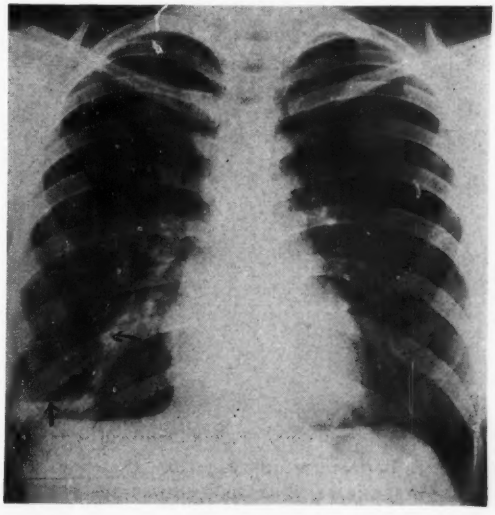


Fig. 7.—Case 5. Large, thin-walled cyst with fluid level, right lower lung field.

rubbery part of the mass was composed of multiple small mucus-containing cysts which were lined by ciliated pseudo-stratified columnar epithelium.

The patient made an uneventful recovery from operation.

CASE 5.—L. M., a girl, aged 16 years, was admitted to the hospital on Feb. 2, 1950. She had pneumonia at the age of 18 months, was said to have had whooping cough 3 times in childhood, had a chronic cough from 2 until 4 years. She was then well until February, 1949, when she had pneumonia in the right lung, and this recurred in October, 1949, and in January, 1950. She raised about one-half ounce of mucopurulent sputum per day, but had not had hemoptysis. On examination she was in good general condition; there was slight dullness with decreased breath sounds at the right base posteriorly.

Roentgenograms (Fig. 7) showed a large thin walled cyst with a fluid level in the right base posterolaterally.

A diagnosis of intralobar sequestration of the right lower lobe was made.

At operation the lower lobe was adherent to the parietal pleura. The posterolateral portion of the lobe was filled by a cyst, 8 cm. in diameter, and this part of the lung was yellow-pink in color and devoid of pigment. Just posterior to this area was a rubbery ovoid structure, of similar color, 5 cm. in length, connected to the surface of the lobe by a short, thin pedicle. Passing to this appendage was an artery 3 mm. in diameter rising from the seventh intercostal artery. There was no accompanying vein. No other anomalous artery was found entering the lower lobe. Dissection lobectomy was done.

Examination of the specimen (Fig. 8) showed that the large intralobar cyst was trabeculated, had multiple bronchial connections, and was lined by ciliated pseudostratified epithelium. The appendage was made up of many small cysts containing thick mucus, and the walls contained bronchial elements. Sections of the pedicle demonstrated that there was no bronchial connection with the lung, but the pedicle was traversed by multiple large vessels. It is considered that this is an example of both extra and intralobar sequestration in which the blood supply to the accessory lung was derived from an intercostal artery and in the absence of an accompanying vein passed on through the pedicle to supply the intralobar sequestration; thence draining into the pulmonary vein.

The patient made a good recovery from the operation and has been relieved of her symptoms.

SUMMARY OF CASES

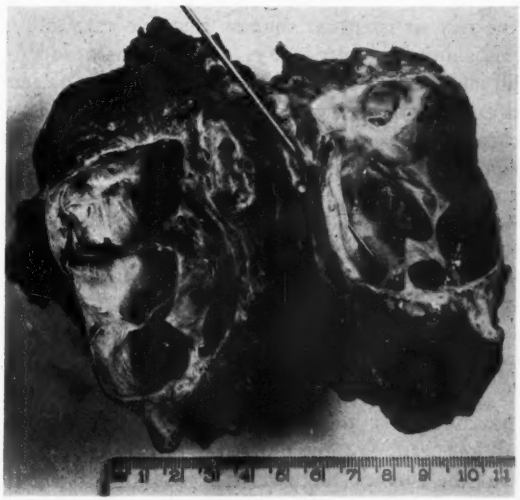
These five patients ranged in age from 16 to 60 years. All complained of chronic cough with sputum, frankly purulent in 4, foul in 1, and 3 patients had had hemoptysis. Four patients showed an abnormality on examination of the chest, usually decreased percussion note, with diminished breath sounds. No patient showed clubbing of the fingers. In all, one or more cysts communicated with the bronchus; in every case the roentgenogram showed a cyst with a fluid level. In three the left lower lobe was involved, and in two the right lower lobe. In two cases the anomalous artery arose below the diaphragm, in two it arose from the thoracic aorta, and in one patient it arose from an intercostal artery. At operation all patients showed a very characteristic picture of a mass of yellowish-pink, nonpigmented lung contained within the posterior part of the lower lobe, rubbery in consistency, and containing one or more cysts.

After clinical and radiographic investigation, the diagnosis in the first case was cystic disease, in the second bronchogenic cyst. In the third case, the man aged 60 years, a diagnosis of intralobar sequestration was considered, but be-

cause the symptoms had come on at 55 years, chronic lung abscess was thought to be a more likely diagnosis. In the last two cases a diagnosis of intralobar sequestration with anomalous blood supply was made with confidence.

All five patients have had a satisfactory result from surgical treatment.

A.



B.

Fig. 8,*A*.—Case 5. Specimen viewed from behind showing lower accessory lung attached to lobe.

Fig. 8,*B*.—Case 5. Lobe opened to show large cyst.

DISCUSSION

As pointed out by Pryce and also by Bruwer and associates this condition is sufficiently common that it is of some importance to physicians and surgeons interested in pulmonary disease. The pathologic anatomy is such that once infection becomes established, it tends to become persistent and lead to chronic disability. Only excision of the diseased segment or lobe is likely to lead to permanent relief of symptoms. A study of these five lower lobes suggests that in only one (Case 5) the bronchial connection with the cyst was primary; in the other four it was probably secondary.

Pryce stated that the oxygenated blood from the anomalous artery drains into the pulmonary vein, and our observations by dissection of the specimens and by perfusion of the artery support this view. Bruwer et al. stated that the vascular connection is with the pulmonary artery. They suggested that further information might be gained by filling the two vascular systems with a plastic solution and then digesting the lung away to leave a plastic model. The same thought had occurred to us, and Fig. 6 illustrates the model obtained. It demonstrates that the distribution of the two arteries is independent, each confined to its own section of the lobe, but from neither source did the plastic pass through the finer ramifications to reach the pulmonary vein, although saline passed through freely when injected from either the pulmonary or systemic artery.

If the observation that the branches of the anomalous artery connect with the pulmonary vein is correct there is a pathway for an unusual type of vascular shunt within the arterial side of the circulation. The size of the artery, the difference in pressure between the aorta and the pulmonary vein, and the ease with which saline can be perfused suggest that the rate and volume of blood flow through this shunt is considerable. This imposes added work upon the left ventricle and may be of some significance in the older patients. The decided improvement in exercise tolerance in the man of 60 years, in spite of the loss of some functioning lung tissue, may have been due to the interruption of this shunt. His lesion was unusual in that there were two arteries coming from the aorta with one accompanying vein draining into the azygos vein, but as the vein was no larger than either of the arteries it is probable that there was also a connection with the pulmonary vein.

Pryce mentions that in extralobar sequestration the blood from the accessory lung commonly drains into a vein connecting with the azygos vein. The discovery of such a vein in the above case of intralobar sequestration is some evidence that intra- and extralobar sequestration have a similar embryological origin and differ only in degree. Case 5, in which both conditions were found in relation to the same lower lobe, also adds some weight to this view.

The clinical and radiographic features of this condition are sufficiently characteristic that the correct diagnosis was made before operation in the last two of these five cases. The appearance of the lung at operation is striking and easily recognized in most instances, which is fortunate, because the operator can then proceed with caution and by demonstrating the anomalous artery avoid the tragedy which has followed inadvertent division of it on three occasions.

SUMMARY

The etiology and pathology of intralobar sequestration of lung as described by Pryce have been reviewed.

Five cases of this condition, all treated by lobectomy, are reported. One of these cases showed an unusual association of both intra- and extralobar sequestration in relationship to the same lower lobe.

Observations which tend to prove that circulation through the anomalous artery constitutes an unusual type of shunt are described.

It is suggested that the clinical and radiographic features of this condition are sufficiently typical to permit a correct preoperative diagnosis. The pathologic condition found at operation is usually recognizable with ease.

Excision of the diseased segment or lobe is a satisfactory method of treatment.

REFERENCES

1. Pryce, D. M.: Lower Accessory Pulmonary Artery With Intralobar Sequestration of Lung; A Report of Seven Cases, J. Path. & Bact. **58**: 457-467, 1946.
2. Pryce, D. M., Sellors, T. H., and Blair, L. G.: Intralobar Sequestration of Lung Associated With an Abnormal Pulmonary Artery, Brit. J. Surg. **35**: 18-29, 1947.
3. Bruwer, A., Clagett, O. T., and McDonald, J. R.: Anomalous Arteries to the Lung Associated With Congenital Pulmonary Abnormality, J. THORACIC SURG. **19**: 957-972, 1950.

THE PHYSIOLOGY AND CYTOLOGY OF PULMONARY EDEMA AND PLEURAL EFFUSION PRODUCED IN RATS BY ALPHA-NAPHTHYL THIOUREA (ANTU)*

CURT P. RICHTER, PH.D.
BALTIMORE, MD.

CLINICIANS and pathologists have observed the appearance of fluid in the lungs and pleural cavities under a great variety of pathologic conditions. Yet despite its common occurrence and great importance, our understanding of the physiology and cytology of pulmonary edema and pleural effusion is still quite limited.

In patients, pulmonary edema and pleural effusion rarely occur unless associated with some complex disease, most notably congestive heart failure, tuberculosis, or pneumonia. Because of this complexity, and because of the critical nature of these diseases, it is almost impossible to develop quantitative methods for studying edema and effusion in the lungs and pleural cavities of living patients. Experimental work on animals, therefore, at present remains our best possible source of knowledge.

For animal work we must have a simple means of producing pulmonary edema and pleural effusion with regularity, yet without doing damage to, or involving any other system of the body; also we must have accurate methods of measuring the amounts of pulmonary and pleural fluids.

These two requirements are met to some extent at least by the use of the "toxic thioureas."[1, 2] Methods of measuring the fluids have now been worked out for the Norway rat.

The "toxic thioureas," of which alpha-naphthyl thiourea (ANTU) has been most extensively studied, are highly toxic for the Norway rat and somewhat less toxic for the dog, domestic pig, cat, and mouse.[3] In all of these species they produced marked pulmonary edema and pleural effusion with great regularity. It is of special interest for the present purposes that they do not produce ascites or edema in any other organ.

The pulmonary edema produced by the thioureas apparently results from a temporary increase in permeability of the lung capillaries. Since the effects are reversible, these drugs apparently produce no lasting damage to the capillaries.[4] In composition, the fluid in the lungs and pleural cavities closely resembles blood plasma; it has a protein content of 3 to 5 per cent and does not contain any red cells.[5]

To study quantitatively the "pure culture" of pulmonary edema and pleural effusion, the ideal method would be to make continuous records on

From the Psychobiological Laboratory, Johns Hopkins Hospital.
Received for publication April 5, 1951.
*Initiated under a contract between the Medical Division, Chemical Corps, U. S. Army, and the Johns Hopkins University, and completed under a research grant from the Division of Research Grants and Fellowships of the National Institute of Health, U. S. Public Health Service.

individual animals of the amounts of fluid that appear in the lungs and pleural cavities. Since this obviously is not possible, recourse has to be taken to another method: that of killing animals at definite intervals after poisoning, weighing their lungs, and measuring the amounts of fluid in the pleural cavities. This procedure, involving the use of a large number of animals, makes the Norway rat the animal of choice because it is so readily available and relatively expendable.

The apparently simple task of measuring pulmonary edema from lung weights proved to be a complicated undertaking. We believe that after many mistakes, we have now devised a simple, reliable, standard technique. A report[6] in 1947 gave the results obtained with an earlier technique.* The present report contains the results of our most recent studies for which the revised and improved techniques were used. The emphasis of these studies has been on the understanding of the formation of pulmonary edema and pleural effusion.

METHODS

A total of 203 adult domesticated rats from our colony and from the Albino Farms, Rutland, Vt., were used for these experiments. With few exceptions, rats weighing between 200 to 300 Gm. were used, since they were known to yield the most constant results. A total of ninety rats were used as normal controls. Many hundred wild and domesticated Norway rats of all ages were used in the preliminary experiments.

It proved necessary to use rats that were essentially free of lung infections (abscesses) and areas of pulmonary consolidation. Although the rats of our own colony had been exposed to a serious epizootic of Type II pneumococcal pneumonia two years before,[7] they proved to have very healthy lungs, only rarely showing any areas of consolidation (less than 1 per cent of the rats). The rats from the Albino Farms also only rarely showed areas of consolidation or abscesses. Rats from several other colonies could not be used because of their defective lungs; in some colonies as many as 50 to 75 per cent showed consolidation.

For two to four days before the experiments, the rats were placed in individual cages, with access to our stock diet† and water ad libitum. They were protected from avoidable noises and disturbances in a room separate from the rest of the colony. Care was exerted to avoid drafts or abrupt changes in environmental temperature.

Alpha-naphthyl thiourea (du Pont) was used for all of these experiments. It has an LD50 of 4.1 mg. per kilogram for domesticated Norway rats of our colony.[8] The ANTU was administered in five different doses: two sublethal doses, 1 and 3 mg. per kilogram, both of which fail to kill any animals; 5, 10, and 50 mg. per kilogram, all three of which kill 100 per cent. The drug was

*These experiments were started during the war in an attempt to devise an antidote for ANTU poisoning in as much as ANTU was being widely used as a rodenticide.

†Graham flour 72.5 per cent, casein 10.0 per cent, skim milk powder 10.0 per cent, butter 5.0 per cent, calcium carbonate 1.5 per cent, and sodium chloride 1.0 per cent.

administered intraperitoneally in olive oil suspension, since it is practically insoluble in water. For all dosages each rat received 1 c.c. of olive oil suspension per 100 Gm. body weight.

To obtain quantitatively reproducible results it was found to be of prime importance to grind the ANTU to very fine particle size before mixing it with the oil and to stir the suspension while injecting the rats. To speed up the injection procedure and thus minimize the rat's excitement, the drug was injected intraperitoneally through an 18-gauge needle, the smallest bore through which the preparation would flow freely.

The following standardized procedure was used in determining the extent of the pulmonary edema and amounts of fluid in the pleural cavities. Since the success of the procedure depends on a number of different operations, the various steps will be described in detail. The rats are etherized in as quick and uniform a fashion as possible. For this purpose a quart Mason jar is used in which the rats can readily be observed at all times; and accordingly, can be removed each time at approximately the same stage of anesthesia. Holding the rats by their haunches during the entire process shortens the time of etherization and greatly reduces the severity of the animal's struggle against the ether.

Once anesthetized, the rats are removed and tied down on their backs on a small operating board. More ether is administered by the open drop method throughout the following procedures:

1. A wide strip of skin is cut away with scissors from the pubic arch to the clavicle and an incision is made into the abdominal cavity from the pubic arch to the sternum, care being taken to avoid entering the pleural cavities.

2. With the first and second fingers of the left hand the viscera are pulled to the side exposing a large free area over the vena cava and abdominal aorta. This area is further exposed by retracting the wall of the abdomen to the opposite side with a fixed hook.

3. The abdominal cavity is checked for the presence of unabsorbed olive oil and for any signs of incidental disease or ascites, and any oil present in the exposed area is thoroughly removed by swabbing. Enough of the vena cava is then freed of fat and peritoneum to provide unobstructed access to the vessel.

4. A 20-gauge needle, attached to a 1 c.c. tuberculin insulin syringe, is introduced into the vena cava and 0.1 c.c. per 100 Gm. of body weight of a solution of heparin sodium (1 c.c. = 10 mg.) is slowly injected to prevent coagulation of the blood.

5. A tear is purposely made in the wall of the vena cava in removing the needle thus allowing the blood to flow freely. All the blood is mopped up with weighed cotton swabs until the flow becomes very sluggish. Then the abdominal aorta is cut across with a pair of scissors and the blood is mopped up again until the flow ceases. The collected swabs are then weighed. This entire process requires about five minutes. The rats usually continue to breathe until well after the aorta has been severed; occasionally they stop breathing before section of the aorta and then start breathing again afterward. Six swabs, each weighing 200 to 250 mg., are used for mopping up the blood.

When blood is desired for hematocrit or cytological studies it is withdrawn from the vena cava through the needle used for introducing the heparin sodium. The tuberculin syringe is removed from the needle and replaced with a 10 c.c. syringe. As much as 12 c.c. of blood may be withdrawn in this way. The bleeding process then continues as described above.

6. The thoracic cavity is entered with care to prevent the loss of fluid into the abdominal cavity. A cut through the ribs is made about 1 centimeter to the right of the midline and continued up to the clavicle. The diaphragm is cut just under the sternum and the ribs are cut from the xiphoid process to the clavicle about 1 cm. to the left of the midline. The sternal flap thus formed is reflected over the animal's head and anchored with a hemostat.

7. Immediately thereafter a curved hemostat is placed just under the heart, occluding all of the cardiac vessels and preventing the flow of the little remaining blood from the heart to the lungs.

8. All of the walls of the thoracic cavity, including the sternal flap, are swabbed in a uniform manner three different times, each time with a new, weighed cotton swab (about ¼ cm. in diameter). These swabs are then weighed to determine the amount of fluid present. When the cavity contains enough fluid to be aspirated, as much fluid as possible is removed with a syringe prior to the swabbing.

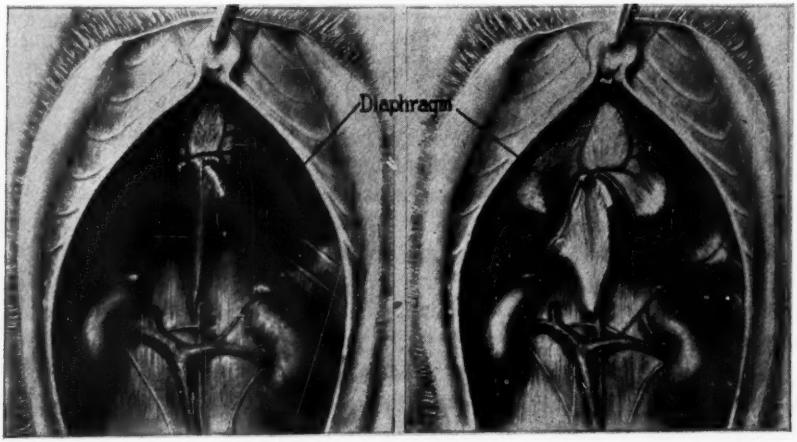
9. The left lung is dissected free and inspected for signs of edema or consolidation. Next a ligature (silk braid) is looped around the lung and tied tightly at the hilum; a cut is made with a pair of fine scissors just proximal to the ligature and the ends of the silk braid are cut at the knot. The surface of the lung is dried lightly on blotting paper before the organ is weighed.

The same process is repeated with the right lung. Owing to its multilobular structure the right lung is more difficult to free. It normally weighs almost twice as much as the left lung.[9]

The pleural effusion swabs are weighed on a torsion balance sensitive to 0.1 mg.; the swabs for the blood weights and lungs are weighed on a balance sensitive to 10 mg.; matched watch glasses are used for the swabs and lungs.

The chief difference between this procedure and that used in our earlier studies lies in the method by which the rats were killed. Formerly the rats were killed by crushing the cervical cord with a pair of pliers. This method had a marked effect on the lung weights and consequently did not permit accurate measure of the fluid in the lungs. In the first place, crushing the cervical cord caused prolonged convulsions in some animals and only mild convulsions in others. Consequently in some rats more blood was forced into the lungs than in others, either as a result of the force of the convulsion or of the longer time interval during which the heart could pump more blood into the lungs. Owing to the varying amounts of blood in the lungs it was never possible to obtain an accurate measure of the amounts of fluid that the lungs contained. In some instances, when crushing the cervical cord caused intracranial and oral bleeding, blood was actually aspirated into the lungs.

Allowing the rats to bleed to death makes it possible to remove all except very small amounts of blood from the lungs. Furthermore, this procedure is carried out on a schedule thus ensuring much more uniform treatment of each rat. A special advantage of the described technique is that opening the chest no longer causes bleeding so that contamination of the pleural fluid with blood is avoided. The use of the ligature of the hilum of the lung prevents the escape of fluid and so further contributes to the accuracy of the procedure.



A. *B.*

Fig. 1.—Drawing of typical eviscerated rats: (*A*) showing the diaphragm of normal rat; (*B*) the diaphragm of a rat that had been poisoned sixteen hours before with ANTU.

RESULTS

A. PLEURAL EFFUSION

Fig. 1 shows the diaphragm of a normal rat and of a rat killed sixteen hours after having received a lethal dose of ANTU (50 mg. per kilogram). The drawings were made just after the rats had been killed and all the intraperitoneal viscera removed. The diaphragm of the normal rat is concave and for the most part in close contact with the walls of the thorax. In marked contrast, the diaphragm of the poisoned rat bulges far down into the abdominal cavity, literally forming a bag of fluid.

The drawing of the sagittal sections in Fig. 2 shows the distribution of fluid in the intact animal when standing in its normal posture. Immediately after the rats were killed with ether, a string was tied tightly around their necks to avoid any changes in the relative position of the organs that might follow the collapse of the lungs and the resulting escape of either air or fluid. Then the rats were placed in a deep-freeze unit, where they were supported in their normal standing posture by straps, and kept there until they were thoroughly frozen in order to prevent any other post-mortem changes.

After freezing, sagittal and transverse sections were cut with a small, thin-bladded bow saw. Wiping the cut surfaces with a wet cloth brought out the outlines of all of the internal viscera in clear detail.

In Fig. 2 the drawing at the left shows a midline sagittal section of a normal healthy rat. The lungs are in close contact with the heart and diaphragm and so fill the entire thoracic cavity. The pleural space is not visible. The drawing at the right shows a midline section of a rat that had received an intraperitoneal injection of ANTU (50 mg. per kilogram) sixteen hours

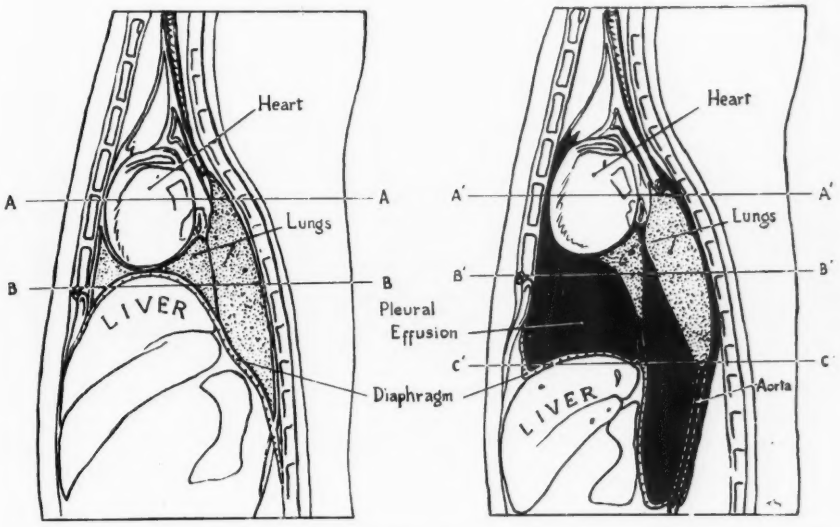


Fig. 2.—Drawing made of typical sagittal sections through the midline of rats frozen in horizontal position in a deep freeze: left, from a normal rat; right, from a rat poisoned sixteen hours before with ANTU.

before being killed. Fluid (solid black areas) fills the greatly distended pleural cavity. The diaphragm is pushed down and away from the heart. The lungs float in the fluid and appear to be collapsed. It is clear that the volume of the fluid in the poisoned rats many times surpasses the volume of the lungs, so that the air space must have been greatly reduced.

Normal Rats.—

Pleural Fluid and Body Weight: Fig. 3 shows the amounts of pleural fluid found in eighty-three normal (untreated) rats, as related to their body weights. The ordinates give the pleural effusion in per cent of body weight, the abscissas body weight in grams. Each dot represents one animal. The solid line is drawn through points obtained by taking the average in each 50-gram interval and represents the proportion of pleural effusion with increasing weight. This remained essentially the same for all rats weighing between 100 and 350 Gm., not surpassing 0.1 per cent in any case. As might be anticipated, the relative amount of effusion was greater in very young animals, averaging 0.12 per cent for

weights up to 50 Gm. and 0.1 per cent of body weight between 50 and 100 Gm. Thus, the amount of fluid in the pleural cavity of normal animals is very small, having a mean of 0.05 per cent of body weight for an adult rat, and a standard deviation of 0.024.

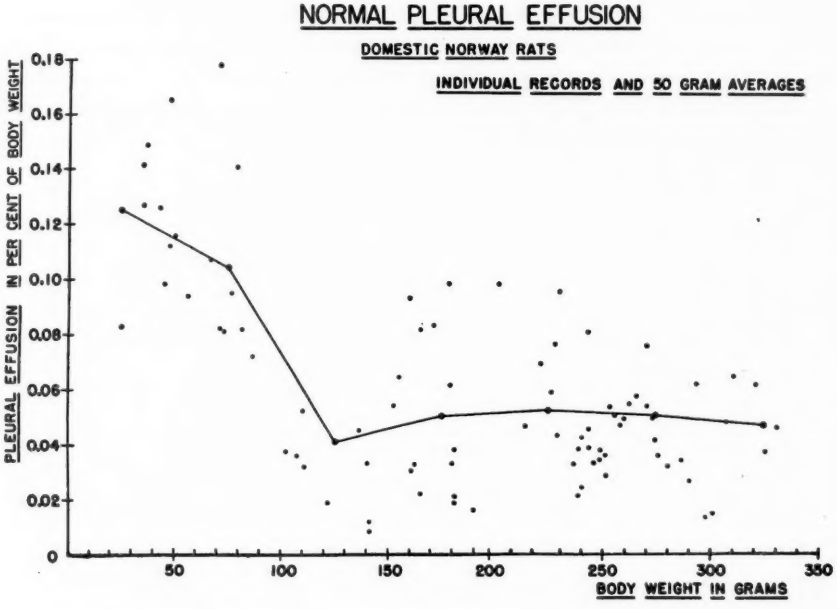


Fig. 3.—Chart showing the amount of fluid in the pleural cavities of individual normal rats at various body weights. Ordinates represent the fluid in per cent of body weight; the abscissas body weight in grams. Each dot represents an individual rat. The solid line connects averages for each 50-gram weight interval.

ANTU Poisoned Rats.—

Onset and Rate of Development of Pleural Effusion: Fig. 4 shows pleural effusion curves for the different dosages of ANTU. The ordinates give the pleural effusion in per cent of body weight; the abscissas time in hours after the ANTU injection. The curves show the averages for one-hour intervals. During the first hour the averages did not increase above the normal 0.05 per cent levels shown in Fig. 3. During the second hour the amount of pleural effusion increased for all except the 1 mg. per kilogram dosage. Thereafter the amount of pleural effusion increased at an almost constant rate for the 3, 5, 10, and 50 mg. per kilogram dosages, reaching an approximate level of 3.5 per cent during the seven to eight hour interval. The 1 mg. per kilogram dosage did not produce an increase in pleural effusion at any time.

Owing to the high rate of mortality of the rats on the 5, 10, and 50 mg. per kilogram dosage after the eighth hour, observations after longer periods of poisoning with these three doses could be made on only a few rats. In our earlier

experiments the pleural effusion reached 5.0 per cent in a number of animals that survived eighteen hours, and 6.3 per cent in one rat that was killed nineteen and one-half hours after having received a 10 mg. per kilogram injection of ANTU.

It is noteworthy that in rats which had received the higher dosages of ANTU and had survived seven to eight hours or more, the thoracic cage appeared to be markedly distended, in some instances literally bulging out from the rest of the body.

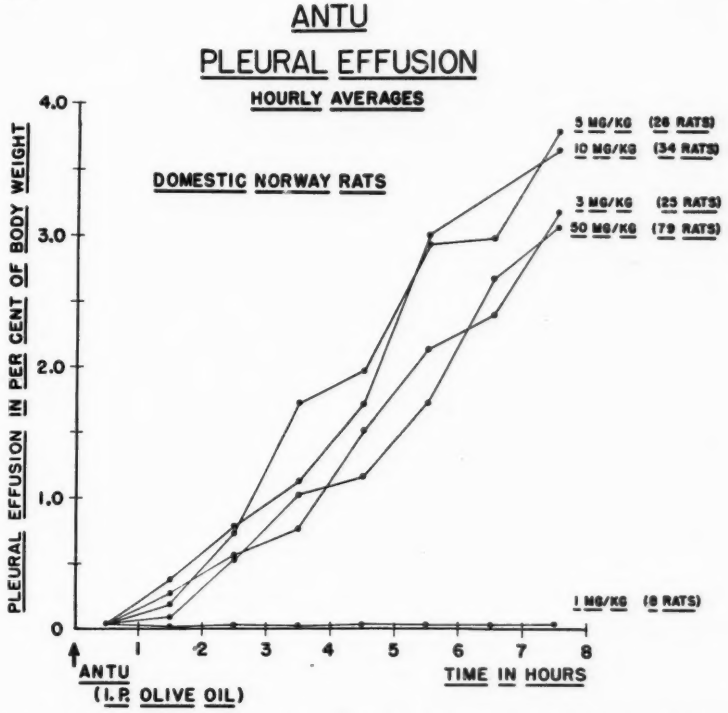


Fig. 4.—Curves showing average amounts of pleural effusion found at hourly intervals after poisoning with five different doses of ANTU. Ordinates represent pleural effusion in per cent of body weight; abscissas time in hours after ANTU was injected.

Since the pleural fluid averages 0.05 per cent of the body weight in normal animals, the high amounts found in the ANTU poisoned rats, 5 to 6 per cent of body weight, represented a hundred-fold increase. The magnitude of the increase can be visualized in another way. In normal rats the lungs occupy a thoracic space that measurement of twenty adult animals showed to average 3 cubic centimeters. In ANTU poisoned animals the maximum amount of pleural effusion occupied 12 to 15 cubic centimeters, a three- to fourfold increase in the thoracic space. Thus, the pleural cavity is capable of a great increase in volume that is probably largely accounted for by a lowering of the diaphragm, but also to some extent to the distention of the thoracic cage. In ANTU poisoned rats the diaphragm apparently is stretched to its full extent.

Duration of Pleural Effusion: Duration of the pleural effusion was studied by the use of a dose that produced marked pleural effusion without killing the rats. The 3 mg. per kilogram dose proved to be very satisfactory for this purpose.

Fig. 5 (top record) shows the individual pleural effusion volume of fifty-two rats sacrificed at varying intervals after administration of a 3 mg. per kilogram dose. The pleural effusion first appeared just shortly after the end

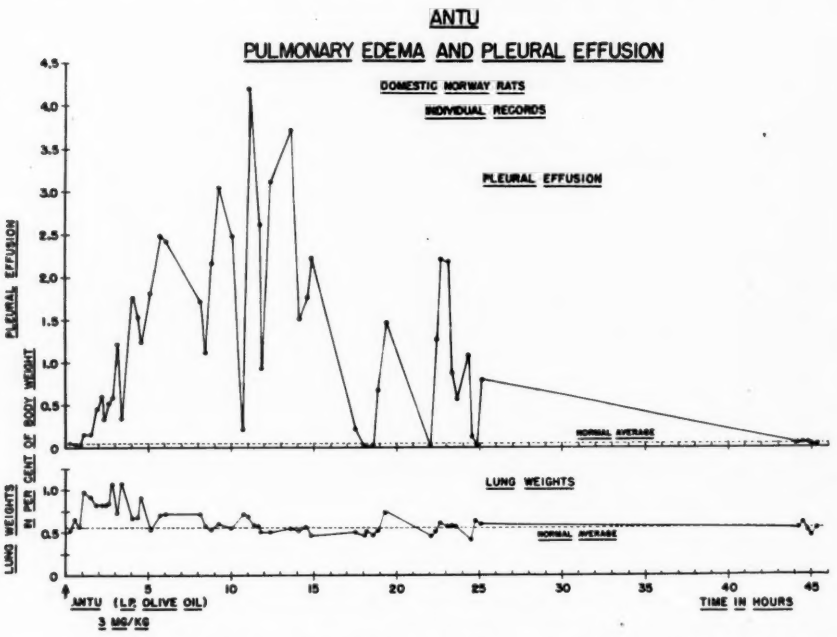


Fig. 5.—Curves showing the pleural effusion and lung weight records for individual animals that received ANTU, 3 mg. per kilogram in olive oil by intraperitoneal injection. Each dot represents an individual rat. The dotted lines give the averages for pleural effusion and lung weights for normal rats ranging in weight from 200 to 300 grams.

of the first hour and had established a fairly constant rate of increase by the end of the second hour. It reached its highest point on the eleventh and fourteenth hours. After the fourteenth hour the amounts of pleural effusion definitely decreased. For the next twelve hours some rats still showed moderate amounts, others scarcely any at all. Five rats examined at forty-four to forty-six hours showed only normal amounts of pleural effusion.

It is noteworthy that during the first fourteen hours the pleural effusion would appear to have increased at the same rate in twenty-three of twenty-six rats. The pleural effusion of the rat examined on the fourteenth hour amounted to 3.7 per cent of the body weight. Statistically, then, it would seem very likely that almost all of the rats examined at later times, would, if they had been examined during the first fourteen-hour period, have shown

equally large amounts of fluid. The fact that many of them showed less fluid, eleven almost none at all, would indicate that during various intervals after the fourteenth hour the pleural fluid must have been resorbed. In some instances the fluid may have been resorbed in only a few hours.

These results agree with the observation recently reported by Courtice and Simmonds.[10] These workers found that homologous dye-plasma introduced into the pleural cavities of rabbits is absorbed at a very rapid rate. These workers concluded from observations on cats that all of the plasma fluid in the pleural cavities is absorbed through the right and left lymphatic ducts.

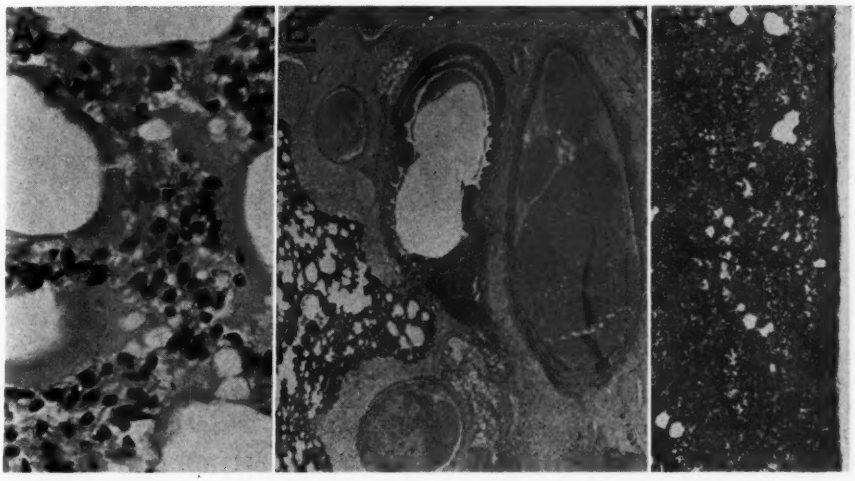


Fig. 6.—Photograph of sections made of the lungs of ANTU poisoned rats. (*A*) lung of rat killed four hours after poisoning with ANTU, 50 mg. per kilogram; (*B*) lung of rat killed eighteen hours after poisoning with ANTU, 50 mg. per kilogram; (*C*) lung of rat in final stage of poisoning with ANTU.

Thus, in summary, these observations have shown that after ANTU poisoning, fluid appeared in the pleural cavities at the same rate with all dosages above and including the sublethal dose of 3 mg. per kilogram. Dosages many times the LD50 did not increase the rate of the production of the fluid. The fact that all of the rats that received the 3 mg. per kilogram dose would have survived even though they had maximal amounts of fluid in their pleural cavities, demonstrates that the mere presence of very large amounts of fluid in the pleural cavity doses not kill the animals.

B. PULMONARY EDEMA

From the work of Latta[4] it is known that fluid first becomes visible in the lymph ducts and perivascular spaces near the hilum, next in the walls of the alveoli, later in the alveoli themselves. The microphotographs of lung sections in Fig. 6 show two of the stages of poisoning with ANTU, 50 mg. per kilogram; (*A*) lung of rat killed four hours after poisoning. The interalveolar

spaces are filled with fluid and the alveoli contain small amounts of fluid; (*B*) lung of rat killed eighteen hours after poisoning. There are large pools of fluid around the vessels. The lymph ducts are markedly distended with fluid; (*C*) lung of a rat in the final stages of poisoning. Fluid fills most of the alveoli except for a few areas where they are distended with trapped air. The alveoli just under the pleura in Fig. 6 *C* seem to be almost completely filled with fluid. In general, the fluid gathers in the alveoli just under the pleura before it appears in the alveoli in other parts of the lung.

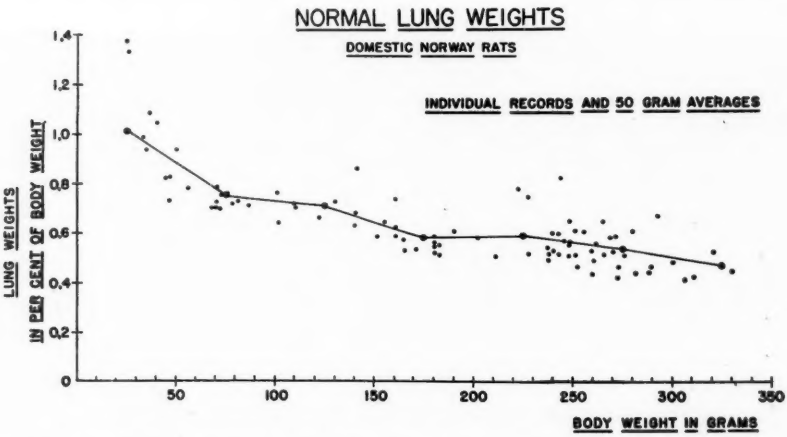


Fig. 7.—Records of lung weights for normal rats of various body weights. Ordinates represent the lung weights in per cent of body weight; the abscissas body weight in grams. Each dot represents the lung weight of an individual rat. The solid line connects the averages for 50-gram intervals.

Normal Rats.—

Lung Weights and Body Weight: Fig. 7 shows the relation of lung weight to body weight for ninety normal rats. Each point represents one rat. Body weight is given in grams on the abscissas and the lung weight in per cent of body weight on the ordinates. The line passes through the average values for each 50-gram range of weight. The proportionate lung weights decreased at a fairly steady rate from 1.01 per cent, for the rats weighing less than 50 Gm., to 0.46 per cent for the 300 to 350 Gm. group, remaining very nearly constant over a body weight range of 150 to 350 Gm. For the 200 to 250 Gm. rats, the mean was 0.56 per cent of body weight with a standard deviation of 0.02.

ANTU Poisoned Rats.—

Lung Weights: Fig. 8 shows the lung weights as per cent of body weight with relation to time after injection of the ANTU for the five different doses. The ordinates show the lung weights in per cent of body weight; the abscissas time in hours. The points on the solid curves represent averages for single hour

periods while the dotted lines show the average lung weights for normal rats of the same weight range. The amount of edema is thus estimated from the excess of these average lung weights over the normal averages.

Rate of Increase of Pulmonary Edema: The rats on the lowest dose, 1 mg. per kilogram, did not show lung edema at any time, while all of the rats on the four higher doses showed a definite edema. During the first hour the average lung weights did not increase in any of the groups of rats; during the second

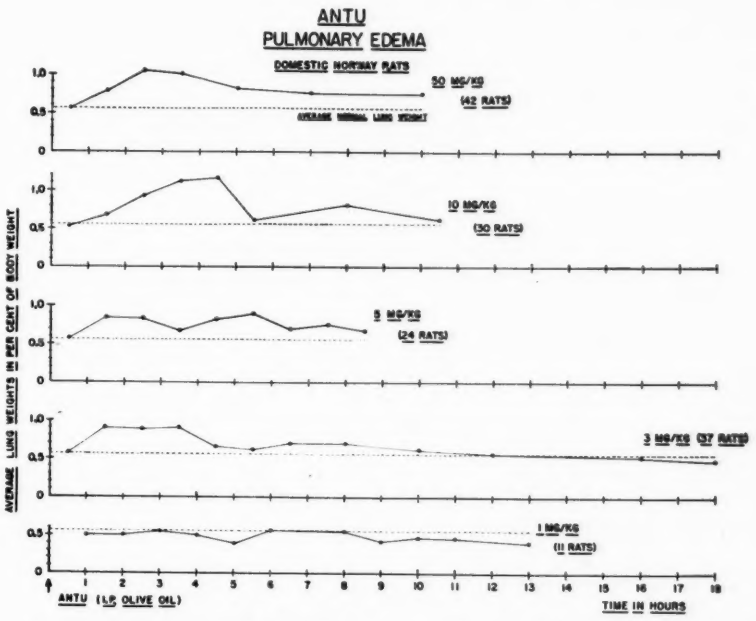


Fig. 8.—Curves showing the average pulmonary edema of rats at hourly intervals after poisoning with five different doses of ANTU. Ordinates represent the lung weights in per cent of body weight; the abscissas time in hours. The dots represent averages for all animals observed within each hour period. The interrupted lines show the average lung weights for normal rats weighing from 200 to 300 Gm. Differences in weight between the lungs after poisoning and the normal average represents the amount of the edema.

hour, however, they increased in all groups; and during the next two to four hours either continued increasing or reached plateau levels. After that the average lung weights decreased again, the remaining level of edema roughly varying in direct proportion to the dosage. The rats receiving the highest dose still had a marked pulmonary edema at the end of ten hours, shortly before many of them began to die, whereas the rats on the 3 mg. per kilogram dose were practically free of pulmonary edema at this time.

The edema amounted to 0.5 per cent of body weight in some instances; in others to only about 0.3 per cent. This means that the weight of the fluid in the lungs at its highest level, was approximately equal to the weight of the lungs.

It should be noted that the changes in lung weights as reported here are based on weighings performed only after the lungs were freed of blood by the technique described for bleeding the rats to death. Since many workers do not follow this procedure, the two records shown in Fig. 9 are presented from our earlier experiments in which we killed the rats by methods other than bleeding. These observations were made on recently trapped wild Norway rats but the results may be compared with those obtained in domesticated rats since they have about the same proportionate lung weights and essentially the same LD50 for ANTU. The dotted horizontals give the average lung weights for normal rats and the bars represent lung weights for the individual experimental rats. In these experiments the rats were given 10 mg. per kilogram of ANTU intraperitoneally in olive oil, and then at various intervals they were killed by crushing the cervical cord. Their lungs were then removed either at once or after thirty to sixty minutes.

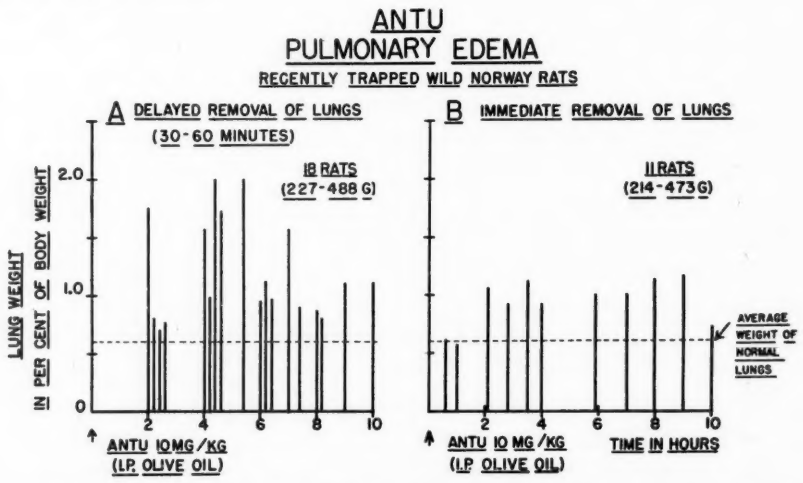


Fig. 9.—Bar graphs showing the lung weights for rats poisoned with ANTU, 10 mg. per kilogram, but not exsanguinated; (*A*) rats that were not autopsied for thirty to sixty minutes after being killed; (*B*) rats that were autopsied as soon as possible after being killed. Each bar represents an individual rat. The dotted lines give the average weight for lungs for normal rats of the same body weight range.

Fig. 9*A* shows that the rats autopsied after a delay had lung weights varying over a very wide range, with differences as much as fourfold. These inconsistent weights probably resulted from the indeterminate amounts of blood pumped into the lungs after the cord was crushed. Fig. 9 *B* shows the greater uniformity in weights of lungs removed as soon as the rats were killed. The increase in lung weights produced by ANTU is clearly demonstrated, but the decrease that occurs after the third and fourth hour in our present experiments was not observed. Presumably the blood in the lungs masked this decrease.

Thus, in summary these observations have shown that after ANTU poisoning, there was marked pulmonary edema for a period lasting from two to six

hours. After several hours, depending on the dosage, some or all of the excess fluid left the lungs. The edema was maintained longest in rats that received the largest doses.

It is likely that the fluid that left the lungs was contained in the lymph ducts, perivascular spaces, and alveolar walls, from which it could readily be absorbed through the right and left thoracic ducts or ultimately be aspirated to the pleural cavities. This will be discussed later. On the other hand it is likely that the fluid remaining in the lungs of rats with the higher dosages of ANTU was contained in the alveoli and alveolar ducts from which places, according to the recent results of Courtice and Simmonds,[11] it probably would not be absorbed for several days.

Fluid does not fill many of the alveoli, or the bronchi and trachea until just before death. In some instances, large amounts of fluid leave the trachea after death, literally forming pools around the heads of the dead animals.

C. THE INTERRELATIONSHIP OF PULMONARY EDEMA AND PLEURAL EFFUSION

After separate consideration of the formation of pulmonary edema and pleural effusion, it is now possible to investigate how they are related—to establish whether fluid appears in the lungs and pleural cavities simultaneously or in sequence. This is significant in order to be able to determine whether the pleural fluid comes from the lungs or whether it comes from the visceral or parietal pleura.

For this purpose, poisoned rats were killed and autopsied at frequent intervals during the first three hours after ANTU injection.

Onset of Effect: Fig. 10 exhibits the pleural effusion and lung weight curves for four doses of ANTU (3, 5, 10, and 50 mg. per kilogram) with each point representing the sacrifice of an individual rat. Average lung weights and pleural effusion in normal rats, and their standard deviations, are indicated by dotted lines.

Fig. 10*A* gives the curves for the rats on the 3 mg. per kilogram dose. It shows that the lungs of rats killed at thirty-three and fifty minutes were slightly heavier than the normal average. However, since these weights fall within the standard deviation they can have only a doubtful significance. During the same time, the pleural effusion remained within the average normal levels. By one hour and seven minutes, the lung weights had increased to 1.0 per cent of body weight, which represented almost a maximum increase. In the same period of time the pleural effusion increased to 0.15 per cent, which is only about one-fortieth of the maximum capacity of the pleural cavities. The pleural effusion did not show a marked increase until near the end of the second hour.

Fig. 10*B* gives the record for the rats that received the 5 mg. per kilogram dose of ANTU. Here again the lung weights showed doubtful increases during the first hour, and a near-maximum increase just after the end of the first hour, when the pleural effusion still showed only the slightest increase, if any. The pleural effusion did not show a marked increase until the early part of the third hour.

Figs. 10*C* and *D* give the records for the rats that received the 10 and 50 mg. per kilogram dose, respectively, again showing that the lungs became well-filled with fluid before appreciable amounts of fluid entered the pleural cavities. However, it should be noted that the increase in both lung weight and pleural effusion occurred more gradually on the higher doses.

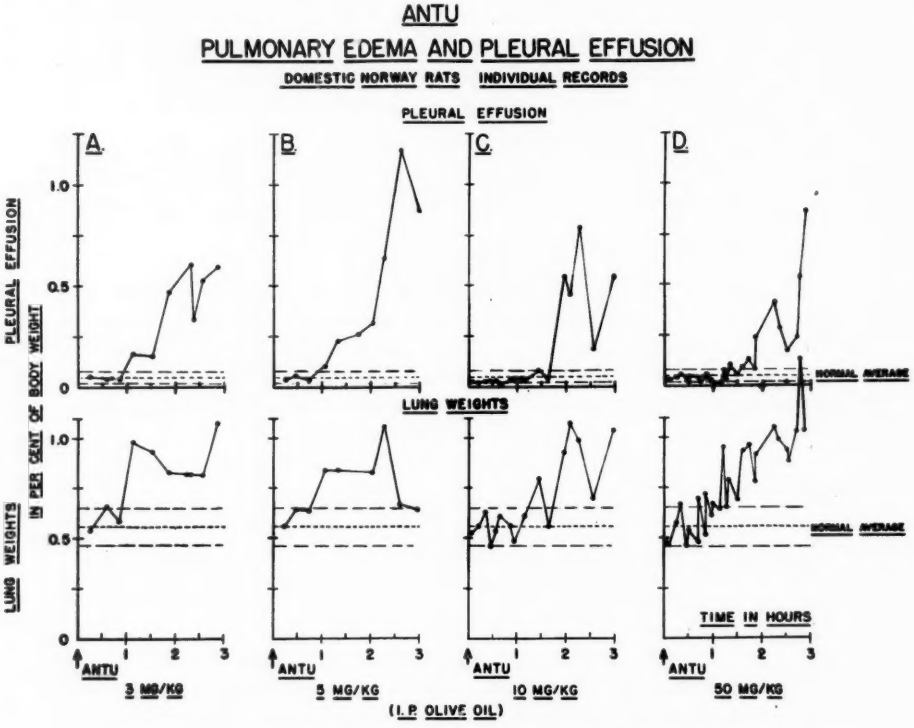


Fig. 10.—Curves showing the temporal relationship between the appearance of pulmonary edema and pleural effusion after various doses of ANTU. Each pair of dots represents data from a single rat. The interrupted lines give the average level and its standard deviation for normal rats.

A study of the curves of Fig. 5 shows that for rats on the 3 mg. per kilogram dose, the pulmonary edema began to recede during the fourth hour, at the time that the pleural effusion was increasing at a very rapid rate. The records for the rats on the other doses show essentially the same relationship.

In summary these observations indicate that after ANTU poisoning, pulmonary edema develops before any appreciable amount of fluid appears in the pleural cavity, and conversely, that the pulmonary edema begins to recede about the time that large amounts of fluid enter the pleural cavity.

These observations indicate that fluid does not appear in the pleural cavities until the lungs have become well filled. We may conclude that the pleural fluid

probably comes from the lungs rather than from the visceral or parietal pleurae. In other words the drug affects the permeability of the capillaries of the lungs only, not of those in the pleura or any other parts of the body. Drinker[5] has pointed out that the lung capillaries are particularly assailable also by anoxia, the chief reason being that these capillaries get their oxygen directly from the air that comes into contact with them, whereas the capillaries of other parts of the body get their oxygen from the common pool of arterial blood supply.

On the basis of clinical and experimental observations, Graham concluded in 1921 that the pleural fluid comes from the lungs.[12] He showed that respiration plays the most important part in the shift of fluid from the lungs to the pleural cavity. According to his thesis, the negative pressure in the thorax of an individual with edematous lungs suffices during the inspiratory phase to aspirate fluid from the lungs to the pleural cavity. The deeper the inspirations the more fluid finally gets aspirated to the pleural cavity. The fluid does not actually leave the lungs during the inspiratory phase, but is brought close to the pleural surface, from where during the following expiration, through shrinking of the lungs, the fluid is pressed out into the pleural cavity.

Graham does not mention through what channels he believes the fluid flows from the lungs to the pleural cavity. Within the lungs it is likely that much of the fluid is conducted to the pleurae through the lymph ducts. Maximow and Bloom state that when for any reason the lymph ducts that lead to the hilum nodes become blocked, fluid flows through the lymph ducts that follow the veins to the pleurae.[13] They state also that valves in the lymph ducts prevent the fluid from flowing back into the lungs.

Early after poisoning with ANTU the rats show changes in breathing, first a mild dyspnea, later heavy deep labored inspirations, strictly of the thoracic type.

Thus, if we apply to the ANTU poisoned rats, the line of reasoning used by Graham, it would seem likely that progressively as the fluid appears in the lungs, or as the air spaces around the capillaries become decreased, breathing becomes deeper. Consequently, with each inspiration fluid is aspirated through the pleura and out into the pleural cavity. Once the fluid gets into the pleural cavity it cannot return to the lungs. The more the lungs become compressed, the smaller the breathing areas become, and as a result the more exaggerated the inspiratory efforts become. In this process all the excess fluid that can leave the lungs becomes aspirated into the pleural cavity. This may explain the decline of the edema that was reported above. It is unlikely that fluid that has already crossed to the alveolar spaces will be forced back into the lungs. The amounts of fluid that get into the alveoli probably determines the fate of the rats.

D. BLOOD VOLUME

Normal Rats.—

Blood Weight and Body Weight: The curve in Fig. 11 shows the amount of blood that was obtained from eighty-six normal rats of different body weights.

Ordinates represent the blood weight in per cent of body weight, the abscissas body weight in grams. Individual points on the curve represent averages for body weight ranges of 50 Gm. It will be seen that the blood weight is essentially constant in relation to body weight for rats between 100 and 250 Gm. As in the case of the lungs, the relative weight of these essential tissues is greater in the younger (small) animals, and distinctly less in animals weighing over 300 Gm. (with their greater proportion of body fat). For the 200 to 299 Gm. rats the mean was 3.5 per cent of body weight, with a standard deviation of 0.37, while in rats up to 50 Gm. the blood represented an average of 4.6 per cent of body weight.

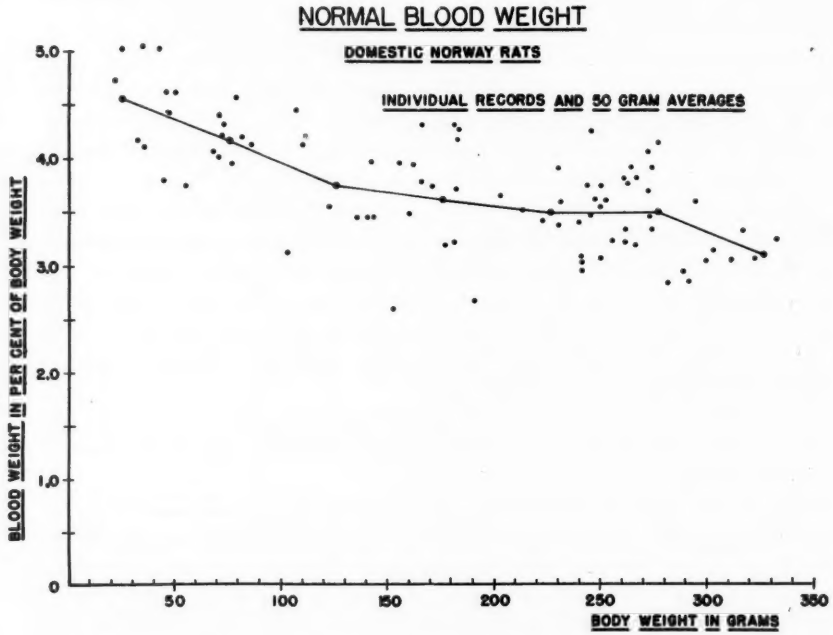


Fig. 11.—Chart showing the amounts of blood obtained by bleeding normal rats to death, (blood swabbed after cutting vena cava and abdominal aorta). Each dot represents the blood weight for one rat. The solid line connects the average blood weights for each 50-gram interval.

These weights were determined by the method of swabbing with cotton as described previously. They fall short of determinations made by other workers, presumably because the method does not assure complete withdrawal of the blood. Some workers have reported a total blood weight of 4 per cent; however most of them give values near 6 per cent.[14]

ANTU Poisoned Rats.—

Blood Weights: Fig. 12 shows the blood weight curves for the rats poisoned with the five different dosages of ANTU. Ordinates give the blood weights

in per cent of body weight; abscissas time in hours after the injection of ANTU. The points on the curves represent averages of each hour up to nine hours; after that averages of two- to three-hour periods. As might have been anticipated from the other data, the blood weights of the rats on the 1 mg. per kilogram dose remained entirely unaffected by the drug. The blood weights of the rats on the 3 mg. per kilogram dose decreased from 3.6 per cent to 2.5 per cent in the course of five hours, thereafter rising to more than 3 per cent. On the three higher doses, the blood weights decreased from levels near 3.5 per cent to a level near 1.0 per cent in seven to ten hours. A comparison of all four curves with those for the pleural effusions in Fig. 4 and Fig. 8 shows that the blood weights decreased roughly in proportion to the increases in pleural effusion in the first five hours.

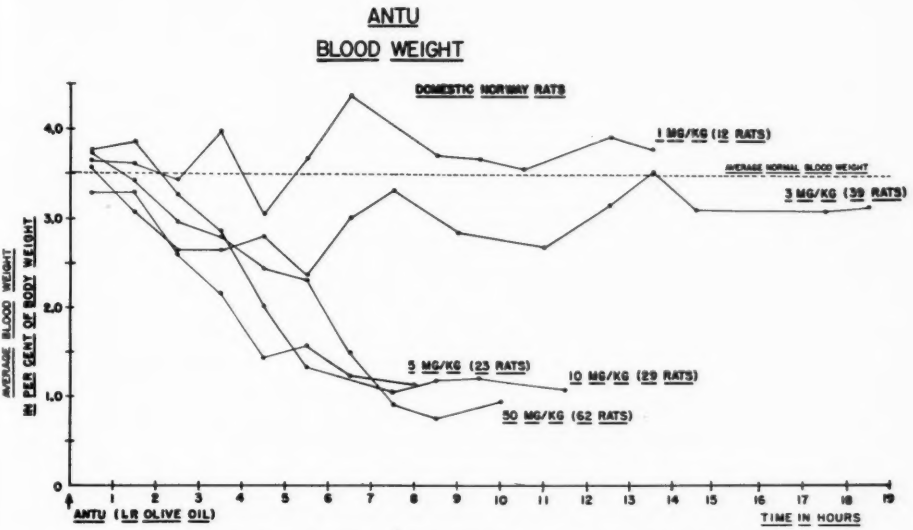


Fig. 12.—Curves showing the average amount of blood obtained by bleeding ANTU poisoned rats to death. Ordinates represent the blood weight in per cent of body weight; the abscissas time in hours. Each dot represents the average for rats observed during each hour after poisoning. The curves are given for five doses of ANTU.

At the time when the blood had been reduced to 1 per cent of the body weight it had a dark color and a viscous consistency. Again as might be anticipated, hematocrit determinations (Wintrobe) showed that the blood began to become concentrated at about the same time as fluid first appeared in the pleural cavities and that thereafter the concentration and pleural effusion increased at much the same rate, while there was a corresponding decrease in blood weight. Fig. 13 exhibits hematocrit values of the rats on the 5 mg. per kilogram dose of ANTU. Fig. 14 shows the hematocrit values of the rats that received the sublethal dose of 3 mg. per kilogram.

Thus, in summary, these observations show that after ANTU poisoning, the large amounts of fluid that fill the lungs and pleural cavities have come to a large extent from the extracellular fluid of the blood. However, in instances in which the fluid in the lungs and pleural cavities amounts to 4 to 6 per cent of the body weight, the approximate equivalent of the total blood volume, it is clear that some of the fluid must also come from the interstitial sources of the extracellular supply.

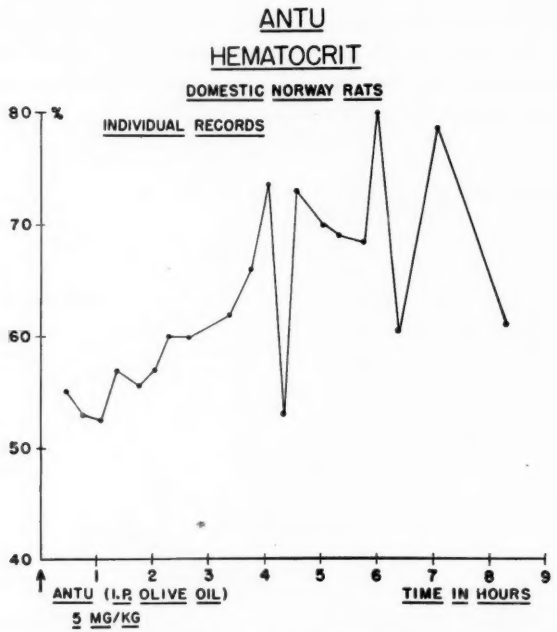


Fig. 13.—Curves showing the hematocrit readings for individual rats at various intervals after receiving 5 mg. per kilogram of ANTU by intraperitoneal injection.

CHEMISTRY AND CYTOLOGY OF THE BLOOD AND PLEURAL EFFUSION OF ANTU POISONED RATS

Chemical and cytologic studies of the blood and pleural effusion were not made at regular intervals after poisoning with ANTU. This will be done in a later study. Observations were made only on a small number of animals that were killed and autopsied about six hours after having received a 50 mg. per kilogram dose of ANTU. However, the incomplete data thus obtained may help to throw some further light on the characteristics of the pleural effusion and blood of ANTU poisoned rats and of their interrelationships.

Table I shows that the content of sodium and potassium in the pleural fluid of ANTU poisoned rats is essentially the same as in the blood serum of normal rats.

Table II shows that the protein and total nitrogen content of the pleural effusion was high, in fact about as high as that of the blood plasma, either of normal or of ANTU poisoned rats.

Table III shows that the white blood cell count of control normal rats averaged 13,630, which is higher than the counts of 11,556 reported by Scarborough,[15] and 11,931 by Wills and Mehta,[16] but lower than the count of 18,819 reported by Thewlis and Meyer.[17] In the ANTU poisoned rats the count increased to 17,455, which may represent a significant increase over the average for normal rats. The count for the pleural effusion was very much lower, 1,770; in some rats it was as low as 700.

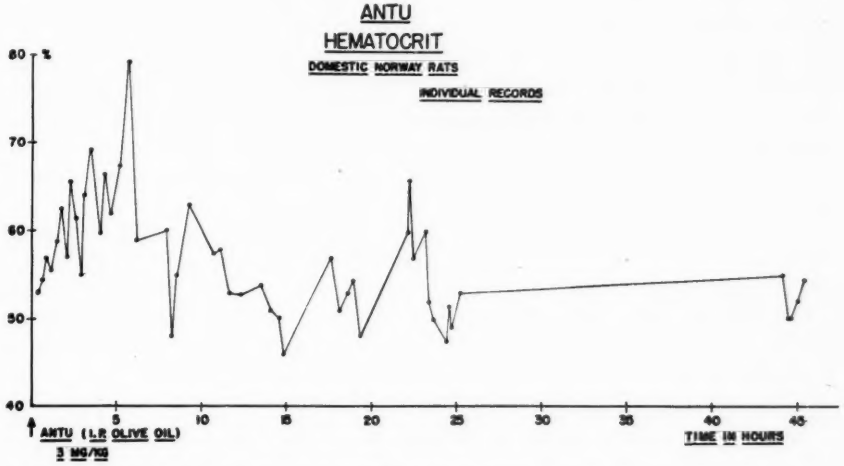


Fig. 14.—Hematocrit readings for individual rats in various intervals after receiving 3 mg. per kilogram of ANTU, by intraperitoneal injection.

TABLE I. AVERAGE SODIUM AND POTASSIUM CONTENT OF BLOOD SERUM AND PLEURAL EFFUSION

	SODIUM MEQ/1	POTASSIUM MEQ/1
Normal Rats (8)	144.1	4.6
Blood serum	(139.6-148.3)	(3.7-4.8)
ANTU-poisoned rats (5)	136.0	4.1
Pleural fluid	(129.0-145.0)	(3.4-4.3)

TABLE II. AVERAGE SPECIFIC GRAVITY AND PROTEIN CONTENT OF BLOOD PLASMA AND PLEURAL EFFUSION

	SPECIFIC GRAVITY	PROTEIN GRAMS PER CENT	TOTAL NITROGEN GRAMS PER CENT
Normal Rats (8)	1.024	5.91	1.042
Blood Plasma	(1.023-1.026)	(5.5-6.5)	(0.926-1.168)
ANTU-Poisoned Rats (8)	1.024	5.81	--
Blood Plasma	(1.021-1.028)	(4.8-7.2)	
Pleural Fluid	1.020	4.74	0.675
	(1.018-1.022)	(3.8-5.2)	(0.604-0.734)

TABLE III. AVERAGE CELL CONTENT FOR BLOOD AND PLEURAL EFFUSION

	W.B.C.	MONO-CYTES	LYMPHO-CYTES	NEUTRO-PHILS	EOSINO-PHILS	JUVE-NILES
Normal Rats (11)	13,630	0	70.4	25.7	3.0	0
Blood	(5,650-29,250)	–	(44-83)	(14-49)	(1-7)	–
ANTU-Poisoned Rats	17,455	0	50.0	47.0	1.0	2.0
Blood (18)	(6,050-29,550)	(0-1)	(38-56)	(43-58)	(0-1)	(0-5)
Pleural Effusion	1,770	2.3	76.4	3.5	14.8	3.0
(15)	(700- 3,925)	(0-10)	(48-96)	(0-14)	(3-40)	(0-8)

The next five columns give the differential count of the white blood cells. In the blood of normal rats the percentages of lymphocytes were almost three times as high as that of the neutrophils and there were only a few eosinophils. In the blood of ANTU poisoned rats the percentage of lymphocytes was reduced, and correspondingly the percentage of neutrophils was increased.

The pleural effusion contained a high proportion of lymphocytes, almost no neutrophils, and many eosinophils. These results show that lymphocytes and eosinophils pass into the pleural cavity very readily, but neutrophils pass only in very small numbers if at all.

BEHAVIOR CHANGES

During the first thirty to sixty minutes after poisoning the animals tended to become less active. Thereafter they sat curled up in a corner of their cage and neither ate nor drank, until they were sacrificed or died, that is providing they received a lethal dose. When they received a sublethal dose they started to eat and drink, and to become active at varying times after the eighth to tenth hours.

OTHER PHYSIOLOGICAL CHANGES

At the same time when fluid began to fill the lungs, body temperature dropped sharply,[2] gastric evacuation was delayed,[18] and the rats became anuric.[19]

GENERAL SUMMARY OF DISPOSITION OF EXTRACELLULAR FLUID AFTER ANTU POISONING

On the basis of the results of the present studies, and of the work of Drinker,[5] Drinker and Hardenbergh,[20] Latta,[4] Graham,[12] an attempt may now be made to give a schedule of the events involved in the disposition of the extracellular fluid after it leaves the lung capillaries of ANTU poisoned animals.

1. The fluid surrounds the capillaries and flows through the interalveolar spaces until it reaches the lymph ducts and is absorbed.

2. In the lymphatic ducts it is carried toward the hilar nodes and from there to the right and left thoracic lymph ducts that lead to the subclavian veins.

3. The fluid very soon appears in large amounts in the perivascular spaces, forming pools of fluid that surround not only the blood vessels but the lymphatic ducts. How the fluid gets from the lymphatic ducts to these spaces is not known. At the hilum these fluid-filled spaces are readily visible through the pleura.

4. Extracellular fluid leaves the capillaries faster than it can be removed by the right and left thoracic lymph ducts. As a result the fluid is forced to flow either into the alveoli or in the opposite direction in the lymph ducts to the pleura.

5. Areas of contact between the air and the lung capillaries are greatly reduced, partly by fluid that surrounds the capillaries, partly by fluid that is present in the alveoli. Both ventilation and gas exchange becomes impaired, and breathing becomes deeper.

6. The deeper inspirations increase the negative intrathoracic pressure and fluid in the lungs near the pleura is aspirated toward the surface. Valves in the lymph ducts prevent the fluid from flowing back into the lungs; so as the lungs contract with each expiration, fluid is squeezed out into the pleural cavity. However, the anatomy of the transudation process by which fluid gets from lymphatics of the visceral pleura to the pleural cavities remains unknown.

7. The pulmonary edema soon reaches a maximum level—fluid fills the interalveolar spaces, the lymph ducts, perivascular spaces, and many of the alveoli, especially those located near the pleura.

8. The fluid that leaves the lungs with each expiration begins gradually to fill the pleural cavities, surrounding and compressing the lungs, and limiting the space available to them.

9. Owing to the compression of the lungs, and the difficulty of achieving a full inflation, the inspirations progressively become deeper and deeper. Fluid is aspirated at such a rapid rate that the lung edema recedes—that is, less fluid remains in the lymph ducts and perivascular spaces. Fluid that has already entered the alveoli probably stays there since it cannot readily be absorbed.

10. At a considerably later stage fluid fills the entire pleural cavity, pushing the diaphragm to its limit, well down into the abdominal cavity, and distending the thorax. Fluid that is still escaping from the capillaries, enters the alveoli, and soon asphyxiates the animal. In the last stage fluid fills the bronchi, trachea, and actually flows from the nose to form a pool around the dead animal.

DISCUSSION

In these studies on rats it was shown how, with the use of ANTU and quantitative methods for the measurement of pulmonary edema and pleural effusion, the course of the flow of extracellular fluid can be followed from the time the fluid leaves the lung capillaries until it becomes distributed to the many parts of the lung, pleural cavities, or returned to the blood stream. It is of special importance that this flow can be thus followed in animals without the complexities that arise in man from presence of infection and defective cardiac function.

On the basis of the results displayed in the charts it should be possible to test various agents, such as morphine, atropine, and various surgical pro-

cedures, such as sympathectomies, that are reported to have an effect on pulmonary edema and pleural effusion. It should also be possible to test various theories about the origin of these phenomena.

The quantitative methods described in this report may also be used for the study of the pulmonary edema and pleural effusion produced by other agents and surgical interferences, such for instance as vagotomies, brain lesions, nephrectomies, exercise, and stress.

Many of the investigations on pulmonary edema and pleural effusion will have to be done on the rat, since it is fairly expendable. Some investigations can be made, however, on the dog, an animal that, like the rat, gives quite constant and reproducible results. Owing to its large size the dog will in some instances lend itself for experiments for which the rat is too small.

A study of thiourea derivatives[21] other than ANTU may throw further light on the underlying mechanisms.

The extent to which results obtained from the rats and dogs can be translated to man is not known, however, it is likely that the mechanisms involved will not be very different. One of the chief anatomic differences is that the rat and dog have a "thin" pleura, whereas man has a "thick" pleura.[22]

It is well known that pulmonary edema and pleural effusion may appear in man quite as quickly as in the rat. Graham[12] mentioned that in patients suffering from a streptococcal pneumonia as much as 1000 c.c. of fluid had been removed from one thoracic cavity within a day or two after the start of the illness.

Observations made by Yamada and co-workers[23] on the pleural fluid of normal healthy soldiers while resting or after exercising may be pertinent at this point. By thoracentesis Yamada was able to draw out varying amounts of fluid (up to 20 Gm.) from as many as 50 per cent of unexercised soldiers; and larger amounts in 70 per cent of exercised soldiers. It is possible, therefore, that fluid appears far more often in the pleural cavities than might have been suspected.

The prominence of the part played by the perivascular spaces in the lung edema produced by ANTU calls attention to the great lack of knowledge about these structures. That little should be known about them probably is not too surprising, since in the normal lung they are not visible. To what extent they resemble perivascular spaces found in other organs, for instance the brain or liver, we have not been able to decide.

The demonstration of large numbers of eosinophils in the pleural fluid also requires special comment. Clinically eosinophilia of pleural fluid has been found in cases of tuberculosis and lobar pneumonia as well as in hypersensitivity diseases, asthma, and Löeffler's syndrome.[24] The observations reported here show that such eosinophilia may appear in the absence of such states. It is noteworthy that an eosinophilia of pleural effusion and a reduction of eosinophils in the blood stream has been produced with some regularity in patients by pneumothorax.[25, 26]

The ability to produce eosinophilia with a fair degree of constancy with ANTU offers an opportunity to study the appearance of eosinophils in the pleural fluid under experimental conditions, free from complications and infections.

Attention may be drawn to the fact that much larger amounts of fluid can be obtained in ANTU poisoned rats than from the blood of normal rats. The ready availability of such large amounts of plasma may be made use of for a number of different investigations.

The exsanguinating technique used in these experiments was adopted at the suggestion of Dr. Arnold Rich, and the results obtained agree with those reported by Durlacher, Banfield, and Bergner on post-mortem edema.[27] They found that when the lungs of rabbits were weighed immediately after death the method of killing did not make much difference in the observed weights; except that the lungs were lightest when the rats were killed with ether. The microscopic examination showed that the alveolar walls were devoid of blood in animals sacrificed by exsanguination or ether. Animals killed with nembutal, magnesium sulphate, or a blow on the head showed great differences in lung weights when they were not autopsied for several hours; animals killed by exsanguination did not show these changes.

Finally, attention should be drawn to one aspect of the effect of ANTU which has not been mentioned: that it produces all the characteristics of shock. That it should show these characteristics is not surprising when we consider the loss of the great amounts of extracellular fluid that the reaction involves. Along with the increase in hematocrit readings, body temperature drops sharply to very low levels, blood sugar increases, anuria sets in, gastric evacuation is retarded, and the animals stop eating and drinking. These clinical aspects will be discussed in detail in a later paper.

SUMMARY

1. Quantitative methods are described for the study of the physiology of pulmonary edema and pleural effusion as produced in the Norway rat by alpha-naphthyl thiourea (ANTU).

2. The amount of moisture in the pleural cavities of normal rats weighing 200 to 300 Gm. averaged 0.05 per cent of body weight; the lung weights averaged 0.56 per cent of body weight.

3. The rats were injected with ANTU at five different doses, 1, 3, 5, 10, and 50 mg. per kilogram of body weight and were killed and autopsied at regular intervals. The first two doses are sublethal, the LD50 being 4.1 mg. per kilogram.

4. In some instances pulmonary edema appeared to begin as soon as thirty minutes after ANTU injection; in most animals it was well started by the end of the first hour. It reached a maximum, 0.5 to 0.8 per cent of body weight, during the second and fourth hours and thereafter either decreased or resulted in death, depending on the dosage.

5. The pleural effusion began after the first hour and increased sharply during the second hour. For the next six to ten hours it increased at a constant

and rapid rate, reaching levels near 3.5 per cent. In some animals it amounted to 5 to 6 per cent.

6. The rate of production of pleural fluid present during the first ten hours was essentially independent of the dosage of ANTU with doses above 3 mg. per kilogram.

7. In rats that received sublethal doses of ANTU the fluid in the lungs and pleural cavities was quickly absorbed within fifteen to twenty hours or less in some instances.

8. The lungs definitely became well filled with fluid before any appreciable amounts of fluid appeared in the pleural cavities.

9. The amount of blood recovered from bleeding normal rats to death averaged 3.6 per cent of body weight for rats weighing from 200 to 299 Gm.

10. After ANTU poisoning these amounts of recovered blood decreased to levels as low as 1.0 per cent, when the blood was very thick and dark in color.

11 The hematocrit increased to levels as high as 80 within ten hours after poisoning.

12. Chemical studies showed that the pleural effusion and blood contained the same amounts of sodium and potassium.

13. The protein content of the pleural effusion averaged 4.44 Gm. per cent (normal for blood 5.91); total nitrogen 0.675 Gm. per cent (normal 1.042).

14. Cytological studies showed that the total number of white blood cells in the blood plasma was somewhat higher in ANTU poisoned rats than in normals. The pleural effusion contained only about one-tenth as many white blood cells as were present in the blood serum of the ANTU poisoned rats. The plasma of normal rats contained about three times as many lymphocytes as neutrophils and only a few eosinophils, whereas in the plasma of ANTU poisoned rats the lymphocytes and neutrophils were present in almost equal numbers, and eosinophils were fewer, if anything. The pleural effusion contained almost no neutrophils, and a correspondingly higher percentage of lymphocytes. It also contained a much higher percentage of eosinophils.

15. The various steps probably involved in the production and control of the pulmonary edema and pleural effusion were discussed.

16. It was pointed out that the curves for the pulmonary edema and pleural effusion may also be used as base lines for testing the effects of various agents, such as vagotomy, nephrectomy, exercise, and stress.

These experiments were carried out with the help of a number of workers who assisted me at various times after the start of the investigation in 1943. Dr. Sally H. Dieke, Mrs. Kathryn H. Clisby, Dr. George S. Allen, Mr. Henry N. Wagner, Jr., Dr. Katherine K. Rice, and Mr. John O. Neustadt helped in the preparation of the manuscript, and Mr. Thomas A. Stebbins and Zolton Yuhasz made the drawings. I am also indebted to Drs. Cecil K. Drinker, Arnold R. Rich, Henry M. Thomas, Jr., Richard Riley and Donald F. Proctor for helpful suggestions and criticisms.

REFERENCES

1. Richter, C. P.: The Development and Use of Alpha-Naphthyl Thiourea (ANTU) as a Rat Poison, J. A. M. A. **129**: 927, 1945.
2. Richter, C. P.: Physiology and Endocrinology of the Toxic Thioureas, Proc. Laurentian Hormone Conf. **II**: 255, 1948.

3. Dieke, S. H., and Richter, C. P.: Age and Species Variation in the Acute Toxicity of Alpha-Naphthyl Thiourea, Proc. Soc. Exper. Biol. & Med. **62**: 22, 1946.
4. Latta, Harrison: Pulmonary Edema and Pleural Effusion Produced by Acute Alpha-Naphthyl Thiourea Poisoning in Rats and Dogs, Bull. Johns Hopkins Hosp. **80**: 181, 1947.
5. Drinker, C. K.: Pulmonary Edema and Inflammation. Cambridge, 1945, Harvard University Press.
6. Richter, C. P., Clisby, K. H., and Allen, G. S.: A Quantitative Study of Pulmonary Edema and Pleural Effusion Produced in Rats by Alpha-Naphthyl Thiourea, Symposium on Military Physiology, Digest Series No. 4, December, 1947.
7. Mirick, G. S., Richter, C. P., Schaub, I. G., Franklin, R., MacCleary, R., Schipper, G., and Spitznagel, J.: An Epizootic Due to Pneumococcus Type II in Laboratory Rats, Am. J. Hygiene **52**: 48, 1950.
8. Dieke, S. H.: Unpublished data.
9. Richter, C. P.: Unpublished data.
10. Courtice, F. C., and Simmonds, W. J.: Absorption of Fluids from the Pleural Cavities of Rabbits and Cats, J. Physiol. **109**: 117, 1949.
11. Courtice, F. C., and Simmonds, W. J.: Absorption from the Lungs, J. Physiol. **109**: 103, 1949.
12. Graham, E. A.: Influence of Respiratory Movements on the Formation of Pleural Exudates, J. A. M. A. **76**: 784, 1921.
13. Maximow, A. A., and Bloom, W.: Textbook of Histology, ed. 3, Philadelphia and London, 1939, W. B. Saunders Co., p. 460.
14. Courtice, F. C.: The Blood Volume of Normal Animals, J. Physiol. **102**: 290, 1943.
15. Scarborough, R. A.: The Blood Picture of Normal Laboratory Animals, Yale J. Biol. & Med. **3**: 267, 1931.
16. Wills, L., and Mehta, M. M.: Determination of Normal Blood Standards for the Nutritional Laboratory's Stock Albino Rat, Indian J. Med. Res. **18**: 307, 1930.
17. Thewlis, E. W., and Meyer, O. O.: The Blood Count of Normal White Rats, Anat. Rec. **82**: 115, 1942.
18. Dieke, S. H.: Unpublished data.
19. Richter, C. P., and Pardee, S. L.: Unpublished data.
20. Drinker, C. K., and Hardenbergh, E.: Acute Effects Upon the Lungs of Dogs of Large Intravenous Doses of Alpha-Naphthyl Thiourea (ANTU), Am. J. Physiol. **156**: 35, 1949.
21. Dieke, S. H., Allen, G. S., and Richter, C. P.: The Acute Toxicity of Thioureas and Related Compounds to Wild and Domestic Norway Rats, J. Pharmacol. & Exper. Therap. **90**: 260, 1947.
22. Miller, W. S.: The Lung, ed. 2, Springfield, Ill., 1947, Charles C Thomas, Publisher.
23. Yamada, S.: Uber die seröse Flüssigkeit in der Pleurahöhle der gesunden Menschen, Ztschr. f. d. ges. Exper. Med. **90**: 342, 1933.
24. MacMurray, F. G., Katz, S., and Zimmerman, H. J.: Pleural-Fluid Eosinophilia. New England J. Med. **243**: 330, 1950.
25. Schwartz, S., and Broadbent, M.: Eosinophiles and Other Components of Pleural Fluids, Tr. Am. Clin. & Climatol. Assn. **55**: 96, 1939.
26. Kabaker, I.: Contribution à l'étude expérimentale des pleurésies à éosinophiles au cours du pneumothorax artificiel, Strasbourg méd. **95**: 277, 1935.
27. Durlacher, S. H., Banfield, W. G., Jr., and Bergner, A. D.: Post-Mortem Pulmonary Edema, Yale J. Biol. & Med. **22**: 565, 1950.

LATE RESULTS IN THE TREATMENT OF PULMONARY TUBERCULOSIS BY THORACOPLASTY

A Review of Two Series

George C. Adie, M.D., William G. Childress, M.D., Herman J. Brezing, M.D., and Donald Taylor, M.D.
Valhalla, N. Y.

NO OTHER collapse measure for the treatment of pulmonary tuberculosis has better withstood the test of time and increased in popularity than has thoracoplasty. Among the reasons for its popularity are its adaptability to selective collapse, the fact that multiple stages may be finished within a relatively short period of time, and prolonged treatments to maintain collapse, as in pneumothorax, are not required. Usually a few months' rest following thoracoplasty is sufficient to stabilize the disease. We prefer to have the patients work up to full activity before leaving the hospital, which usually requires eight to twelve months, and patients are advised not to return to full-time employment for a period of six months after discharge. In this way patients become adjusted to the home environment and are gradually advanced to full activity. Thoracoplasty has been eminently successful in the treatment of chronic disease, such as fibrocaseous ulcerative disease, where extensive destruction has not taken place. Chemotherapy has broadened the field of surgical indications, including thoracoplasty and resection, and, although collapse by pneumothorax is still preferable in some instances, it has declined in popularity. A better understanding of pulmonary physiology and the effects of chemotherapy have reduced the hazards of the operation and made better selection possible. Advances in physiotherapy and exercise techniques have done much to prevent resulting deformity. The high percentage of permanent and lasting excellent results justify confidence in the operation.

RESULTS

Group I.—In 1942 we reported results obtained in the treatment of 146 patients with pulmonary tuberculosis by thoracoplasty, followed for a period of one to eight years.[1] The purpose of this report is to show results of late follow-up on this series, and to report results to date on 188 additional patients treated by thoracoplasty.

In the original report on 146 (one- to eight-year follow-up), 100, 68.4 per cent, were living; 93, 63.7 per cent, had reached a stage of arrest, 8 of these died from unrelated causes; 7, 4.8 per cent, were improved; 8, 5.4 per cent, were unimproved. Forty-six, 31.5 per cent, were dead from all causes; 9 had died from causes other than tuberculosis.

Results of subsequent follow-up on this group of 100 through 1949 (one to seventeen years) show that of 80 living when last heard from, 76 had arrested

From the Divisions of General Surgery and Diseases of the Chest, Grasslands Hospital.
Received for publication May 21, 1951.

or apparently cured disease; 4 had active disease and were curing; and 20 had died, 4 from unrelated causes.

Group II.—From July 1, 1940, to July 1, 1948, 188 patients with pulmonary tuberculosis have received thoracoplasty. Years, number of patients, age, sex, and race are given in Table II.

All patients had advanced disease and had received previous bed rest and special procedures including minor collapse and other treatment as indicated.

TABLE I. FURTHER FOLLOW-UP—ORIGINAL GROUP

NO—146	LIVING—80	DEAD—66
	Followed	53, 36.3% progressive pulmonary tuberculosis
	6 for 17 yr.	
	5 for 16 yr.	
	2 for 15 yr.	13, 8.9% other causes
	3 for 14 yr.	
	6 for 13 yr.	
	15 for 12 yr.	
	17 for 11 yr.	
	2 for 10 yr.	
	9 for 8 yr.	
	3 for 7 yr.	
	3 for 6 yr.	
	4 for 5 yr.	
	4 for 3 yr.	
	1 for 1 yr.	
Total 146	80 (76, 52.0% arrested; 4, 2.7% curing)	66

TABLE II

YEAR OF OPERATION	PATIENTS OPERATED ON	MALE		FEMALE		AGE GROUPS					TOTAL
		WHITE	NEGRO	WHITE	NEGRO	10-20	20-30	30-40	40-50	OVER 50	
1940	11	4	1	6		1	2	4	4		11
1941	26	12	5	8	1	3	4	14	2	3	26
1942	28	10	4	12	2	2	12	6	4	4	28
1943	18	8	1	6	3	1	5	8	3	1	18
1944	15	6	2	5	2		5	5	4	1	15
1945	18	3	3	10	2		8	6	2	2	18
1946	18	4	4	8	2	1	5	10	1	1	18
1947	34	10	3	14	7	8	9	12	5		34
1948	20	8	2	8	2	4	6	4	4	2	20
Total	188	65	25	77	21	20	56	69	29	14	188*

*Total of 414 stages—29 were revision operations.

TABLE III. RESULTS OF FOLLOW-UP—GROUP II

NO. 188	LIVING—150	DEAD—38
	Followed	
	19 for 8 yr.	33,* 17.5% progressive pulmonary tuberculosis
	13 for 7 yr.	5, 2.7% other causes
	12 for 6 yr.	
	12 for 5 yr.	
	14 for 4 yr.	
	17 for 3 yr.	
	35 for 2 yr.	
	28 for 1 yr.	
	150	111† arrested—negative sputum
Total 188		13 apparently well—positive sputum or gastric culture
		31 active—positive smear

*One complicated by meningitis.

†Five nontuberculous deaths in this group.

One hundred eighteen, or 51.3 per cent, of those living in Groups I and II have been followed from five to seventeen years and have arrested or apparently cured tuberculosis, whereas 13, or 5.6 per cent, of this group still have active disease. Of those living and followed less than five years, 64, or 27.8 per cent, have arrested or apparently cured disease. In combining the two groups we find that 194, or 84.3 per cent, of those living or dying from causes unrelated to tuberculosis had or have arrested or apparently cured tuberculosis. Thirteen, or 5.7 per cent, are apparently well but have positive sputum or gastric cultures, and 35, or 15.2 per cent, have active tuberculosis.

COMMENT

Although the number is small and not statistically significant, there were no striking differences noted in results in the various age, sex, or racial groups. Better results in the "good chronic" have generally been observed, and hold true in this series, although nine of ten patients with caseous pneumonic disease have sputum conversion on culture, and one is positive on culture only. All patients had one or more courses of streptomycin prior to and during operation. Poorer results have been observed in giant cavitary lesions, in markedly destructive disease, and where there is tuberculous tracheobronchitis. Similar observations were made by Rubin and Klopstock.[2] Nineteen patients in the series had concomitant systemic diseases, such as diabetes, cardiovascular disease, peptic ulcer, and hyperthyroidism. Twenty-nine had respiratory complications such as asthma, bronchitis, bronchiectasis, pneumonoconiosis, and emphysema. With the use of sulfonamides and penicillin in this series, secondary wound and pulmonary infections were seldom encountered. Streptomycin and other antituberculosis drugs were often used in recent years during the operative period to prevent or reduce postoperative spread. Physiotherapy, including preoperative and postoperative exercises, has been used in recent years with noticeably less chest deformity.

LATE RESULTS REPORTED IN THE LITERATURE

Results in the literature during the last two decades[1, 3-11] reveal improvement in the majority of patients operated upon, although consistency in evaluating results of sputum conversion makes comparison difficult. Reports on sputum conversion, the best evidence of a lasting and permanent result, are often omitted, and, if given, some reports of conversion are based on microscopic absence of the tubercle bacillus on direct smear or on concentrate only. In recent years an increasing number includes the more dependable cultural studies of sputum or gastric washings, or both, and animal inoculation. In the original series, 63 per cent of patients converted on repeated examination of concentrated sputum. Animal inoculation was not routinely done on all. The late results in this series have included sputum or gastric culture in most instances. In the second series of 188, all results are based on conversion of sputum or gastric washings on culture.

In evaluating the late results in thoracoplastry for pulmonary tuberculosis, Dolley, Jones, and Paxton,[7] in 1939, found a total of 1,636 cases reported in

the literature, and 43 per cent were improved. In 1941 Skinner and associates[12] reported that of 100 cases followed from 1924 to 1941, 54 per cent were "apparently cured." Douglass[13] in 1947 reported that 69 of 102 patients subjected to thoracoplasty were classified as "good," which requires that sputum be absent or microscopically negative at the fifth year after operation. Of 168 patients reported by Rubin and Klopstock[2] in 1949, 141 were followed for a period of from two to six years, and of these 63.1 per cent had arrested disease with negative sputum or gastric concentrates on culture. Kinsella and coworkers[14] in 1949 reported that of 613 patients receiving thoracoplasty for pulmonary tuberculosis at Glen Lake Sanatorium, followed from five to twenty-six years, 66.8 per cent were alive, and 88.1 per cent of patients with positive sputum converted to negative "according to the direct examination technique used at the sanatorium over the years covered by the study." Recently, Gutheil, Steele, Cadden, and Sakaguchi[15] reported results of thoracoplasty for pulmonary tuberculosis in 254 patients, followed for two to ten years. Cultures of pulmonary secretions were negative in 193, 67 per cent of patients. Hagn-Meincke[16] reported late results in 420 cases subjected to thoracoplasty at the Oresundshopsital, Copenhagen, Denmark, followed for less than one-half to more than two years. At the end of the observation period, 193, 46 per cent, were classified as "healthy," which included negative cultures of sputum or gastric washings. Follow-up is not sufficiently long in this series to evaluate late results.

SUMMARY AND CONCLUSIONS

From 1932 through July, 1948, 334 patients received thoracoplasty for pulmonary tuberculosis at Grasslands Hospital. Follow-up through 1949 (one to seventeen years) reveals that 230 are living and 104 are dead from all causes. One hundred ninety-four, or 58.0 per cent, attained arrest or apparent cure of the disease, 12 of these died from unrelated causes; 13, 3.8 per cent, are symptom free and positive only on culture of sputum or gastric washings; and 35 have active disease. Results reported here compare favorably with other reports on late results from thoracoplasty and emphasize the competence of thoracoplasty in the treatment of pulmonary tuberculosis. Among the 230 living patients, and including 12 who died from causes unrelated to tuberculosis after arrest of their disease, 84.3 per cent had or have arrested or apparently cured tuberculosis. Late results in thoracoplasty justify its prominent place in the surgical treatment of pulmonary tuberculosis.

REFERENCES

1. Adie, George C., Huested, Lester C., Childress, Wm. G., and Perez, Horacio: Paravertebral Thoracoplasty for the Treatment of Pulmonary Tuberculosis, Surgery **11**: 788-796, 1942.
2. Rubin, Morris, and Klopstock, Robert: Influence of Type of Disease on the Results of Thoracoplasty in Pulmonary Tuberculosis, Am. Rev. Tuberc. **60**: 273-287, 1949.
3. Freedlander, S. O., and Wolpaw, S. E.: Control Group for Studying End Results of Thoracoplasty, J. THORACIC SURG. **6**: 477-490, 1937.
4. Overholt, R. H.: Selective Thoracoplasty With Lung Mobilization, Am. Rev. Tuberc. **37**: 152-173, 1938.
5. Mauer, A., and de Savitsch, E.: Thoracoplasty in Treatment of Pulmonary Tuberculosis, Am. Rev. Tuberc. **38**: 738-745, 1938.

6. Coryllos, P. N.: Surgery of Pulmonary Tuberculosis, Quart. Bull., Sea View Hosp. **1:** 456-475, 1936.
7. Dolley, Frank S., Jones, John C., and Paxton, John R.: Late Results of Thoracoplasty, Am. Rev. Tuberc. **39:** 145-161, 1939.
8. Wagensteen, O. H., Carlson, H. A., and Bowers, W. F.: Partial Thoracoplasty for Pulmonary Tuberculosis, J. THORACIC SURG. **7:** 365-381, 1938.
9. Zuelke, Paul E., Adams, W. E., and Bloch, Robert C.: Thoracoplasty for Pulmonary Tuberculosis, Observations on 32 Patients in the Older Age Group, Am. Rev. Tuberc. **54:** 368-375, 1946.
10. Rudolph, Charles W.: A Review of 244 Thoracoplastic Operations, Med. Bull., Veterans Administration **19:** 1-7, 1942.
11. Shapiro, Reuben, and Munz, C. Walker: Thoracoplasty in the Fifth and Sixth Decades, Am. Rev. Tuberc. **42:** 631-639, 1940.
12. Skinner, George F., MacPherson, L., and Allen, I.: Thoracoplasty for Tuberculosis; Late Results, J. THORACIC SURG. **11:** 54-64, 1941.
13. Douglass, Richmond: Late Results of Thoracoplasty, Am. Rev. Tuberc. **56:** 175-183, 1947.
14. Kinsella, T. J., Mariette, E. S., Matill, P. M., Fenger, E. P. K., Funk, V. K., Larson, L. M., Cohen, S. S., and Nemec, F. C.: Thoracoplasty in the Treatment of Pulmonary Tuberculosis, Am. Rev. Tuberc. **59:** 113-127, 1949.
15. Gutheil, Douglas, Steele, John D., Cadden, A. V., and Sakaguchi, Sanbo: Late Results of Thoracoplasty According to Types of Pulmonary Tuberculosis, Am. Rev. Tuberc. **62:** 645-653, 1950.
16. Hagn-Meincke, F.: Late Results in Four Hundred Twenty Tuberculous Patients Subjected to Thoracoplasty, J. THORACIC SURG. **19:** 837-852, 1950.

THE SURGICAL SIGNIFICANCE OF CALCIFIED PARABRONCHIAL AND PARATRACHEAL LYMPH GLANDS

ELMER R. MAURER, M.D.
CINCINNATI, OHIO

VERY little direct attention has been focused on the surgical significance of calcified lymph glands producing bronchial obstruction with atelectasis, cough, hemoptysis, bronchiectasis, and bronchiolithiasis. The normal distribution of these glands in and about the tracheobronchial tree, particularly at points of bifurcation, permits pressure and bronchial obstruction by these nodes when they become diseased, with consequent enlargement or calcification. The exact mechanism of the production of calcification in lymph glands cannot always be determined. However, it is known that any dying or dead tissue surrounded by living tissue and accessible to body fluids has a tendency to take up calcium salts in the process of healing. Such changes are common following tuberculous infections, histoplasmosis, or chronic suppurative processes. Since such disorders are commonly encountered in the lungs, it is surprising that there is not an even higher incidence of calcification in the filtering tracheobronchial glands. Probably the calcification of most tracheobronchial lymph glands occurs as a result of primary tuberculous infection during childhood.

Tuberculous infection of tracheobronchial or hilar lymph glands as part of the primary complex producing atelectasis, obstructive emphysema, and subsequent bronchiectasis in the lungs of children has been not uncommonly reported in the literature.[1-4] Many instances of bronchoesophageal fistulas resulting from erosion by calcified lymph glands are recorded.[5] Also, case reports of spontaneous cures following extrusion and expectoration of the calcified contents of lymph glands are not unusual.[6] Only recently, however, has the attention of the thoracic surgeon been focused on the possibilities of the surgical management of lesions produced by obstructing inactive calcified parabronchial glands. Head and Moen,[6] in 1948, reported ten cases demonstrating some of the late nontuberculous complications of calcified hilus lymph nodes. In this series only one case of middle lobe obstruction was subjected to open thoracic operation. Buckles,[7] in 1949, suggested a more direct surgical approach to calcified hilar glands producing bronchial obstruction, and emphasized that in the past insufficient importance had been attached to the mere presence of these calcified nodes.

In many instances, the roentgenographic findings of atelectasis, along with a history of cough and hemoptysis, are very properly thought to result from

From the Department of Surgery, College of Medicine of the University of Cincinnati, and the Cincinnati General Hospital.
Received for publication May 23, 1951.

a primary bronchiogenic malignancy until extrabronchial compression with or without erosin by calcified parabronchial lymph glands is demonstrated at operation to be the actual cause of the symptoms and findings.

Final etiological diagnoses, even following endoscopy and bronchography, are often impossible to make preoperatively because of the usual extrabronchial location of the calcified gland producing the bronchial compression. For this reason, also, it is difficult to differentiate these lesions from primary bronchiogenic carcinomas which are not uncommonly found outside of the bronchial wall and can produce bronchial compression and atelectasis without presenting within the lumen.

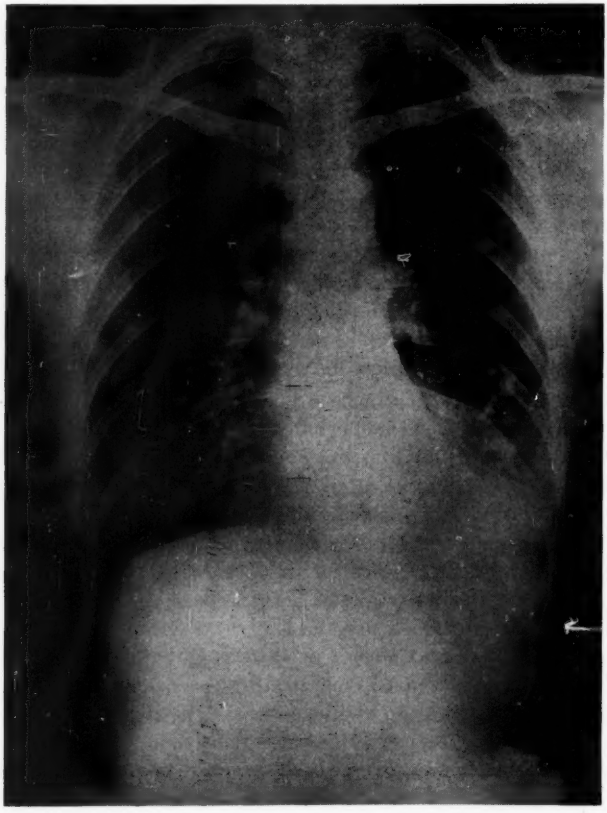


Fig. 1.—(Case 1.) Arrow points to calcification. Note atelectasis in left lower lobe.

As with many other nonmalignant lesions producing obstruction with symptoms simulating carcinoma, surgical excision of the diseased lung along with the calcified lymph glands invariably results in a cure.

To illustrate graphically the practical application of these observations, recent experiences with three patients are presented.

CASE REPORTS

CASE 1.—M. H., a 47-year-old white woman, was admitted to Christ Hospital on Nov. 10, 1950, with a protracted four-year history of cough, hemoptysis, purulent sputum, and constantly recurring upper respiratory infections. The patient had previously been studied in another hospital where bronchographic examination had revealed bronchiectasis in the lower lobe of the left lung. At the time of admission to the local hospital the patient was running a low-grade fever and presented signs and symptoms of a pneumonic infection in the left lower lobe. Routine studies of the urine and blood revealed no abnormalities.

Fig. 2.—(Case 1.) Bucky film reveals three areas of calcification. Middle arrow points to calcified body within lumen of bronchus.

A posteroanterior projection roentgenogram of the chest made on admission to the hospital revealed atelectasis and pneumonia in the lower lobe of the left lung in the area in which bronchiectasis had been previously described. A small calcified lymph gland, to which little significance was attached at the time, was noted in the left paramediastinum (Fig. 1).

Bronchoscopic examination on Nov. 25, 1950, revealed what was thought to be a large, dirty-gray tumor mass arising from the wall of the left main-stem bronchus at a point one and one-half inches distal to the primary carina. The tumor was stony hard, so that a biopsy was difficult to obtain with the forceps. A crunching noise was produced when the forceps was applied. It was obvious at the time of this examination that we were dealing with a calcified lesion which was covered with epithelium and had produced almost complete obstruction of the left main-stem bronchus. Attempts to dislodge the tumor or calcified body by endoscopic manipulation were unsuccessful because of one ramification which could be seen extending into the left upper lobe orifice. Scrapings were obtained from the epithelium covering the calcified body, and on microscopic examination in the pathology laboratory,

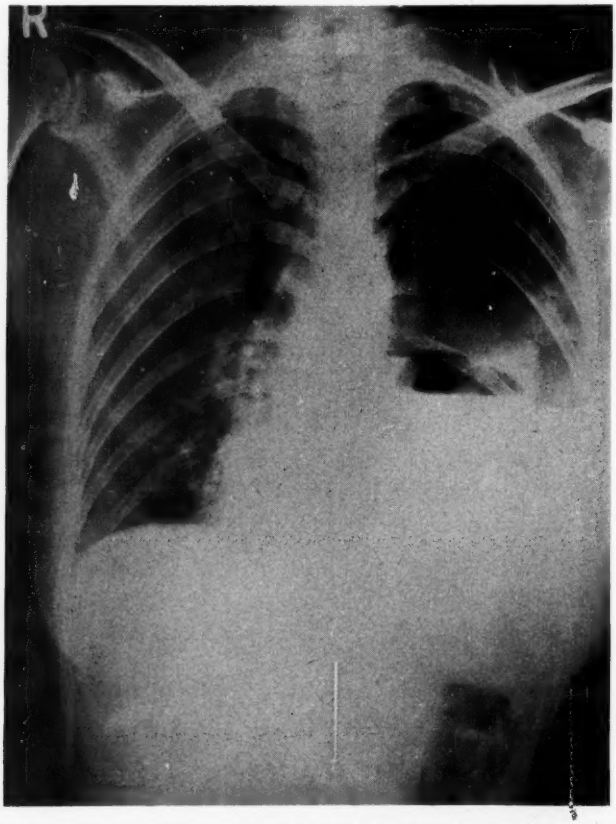


Fig. 3.—(Case 1.) Roentgenogram of chest following left pneumonectomy.

chronic inflammation and polyp formation were described. Bronchial washings were negative for acid-fast organisms and tumor cells. In the differential diagnosis, broncholith and chondroma or osteoma of the bronchus were considered.

A repeat roentgenogram of the chest, posteroanterior projection, using Potter-Bucky technique, was made following the bronchoscopic examination. For the first time three calcified bodies in and about the tracheobronchial tree near the midline on the left were revealed. One calcified body was easily apparent in the lumen of the left main-stem bronchus (Fig. 2).

Because of the location of the calcified body in the left main-stem bronchus in such a position that it could not be dislodged by endoscopic manipulation, and also because of the findings of irreversible changes, namely, bronchiectasis in the lung distal to the point of obstruction, pneumonectomy was recommended.

On Dec. 1, 1950, a left pneumonectomy was performed using the classical individual vessel ligation technique. Dissection in the mediastinum was made tedious because of extensive deposits of scar tissue and the presence of several firm but noncalcified lymph glands about the main-stem bronchus. The patient did well following the operation, and was discharged approximately two and one-half weeks after admission (Fig. 3).

Fig. 4.—(Case 1.) Arrow points to calcification in left main-stem bronchus and anchored in orifice of left upper lobe bronchus. Note anterior calcified parabronchial lymph gland and advanced bronchiectasis in left lower lobe.

Complete dissection of the lung following surgical removal revealed no evidence of tumor. A large broncholith which had the configuration of a Staghorn calculus, such as is encountered in the pelvis of a kidney, almost completely occluded the left main-stem bronchus. One "horn," as was noted at the time of bronchoscopy, extended into the left upper lobe bronchus. A second large calcified gland was situated anterior to the left main-stem bronchus. There was advanced cylindrical and saccular bronchiectasis involving the lower lobe of the left lung (Fig. 4).

COMMENT

The serious significance of the calcified body in the left paramediastinum was not appreciated before the bronchoscopic examination because of the relatively normal roentgenographic findings in the left upper lobe without gross evidence of atelectasis or mediastinal shift. Roentgenograms of the chest using Potter-Bucky technique made following the bronchoscopic examination, however, for the first time revealed three calcified bodies, one of which was thought

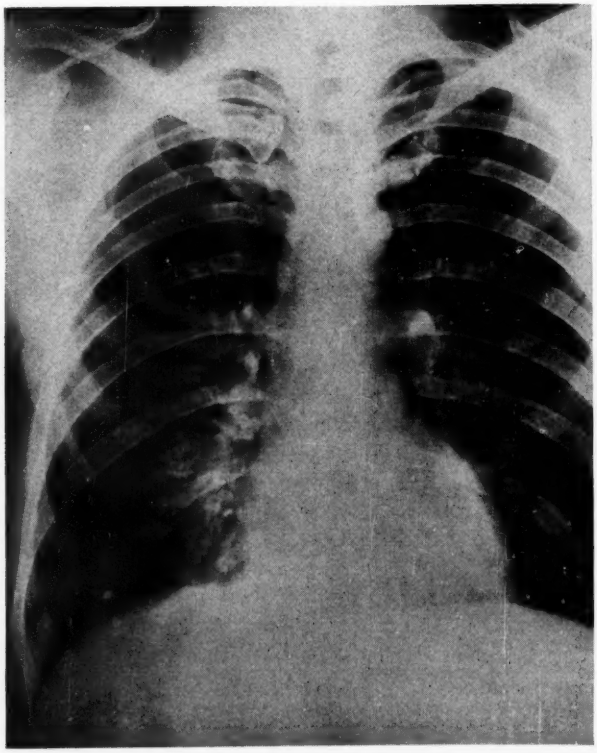


Fig. 5.—(Case 2.) Admission roentgenogram of chest. Arrows point to three calcified lymph glands. Note density right lower mid-lung field.

to be within the lumen of the left main-stem bronchus. This woman had suffered several years with recurrent upper respiratory infections which had been diagnosed as bronchiectasis of the left lower lobe, but there had not been any real understanding of the exact cause of the disease on the left side. This experience emphasizes the importance of an endoscopic examination prior to all bronchographic studies.

CASE 2.—R. N., a 40-year-old white man, was admitted to Christ Hospital on Dec. 17, 1950, because of the incidental finding, by roentgenologic examination, of an infiltrate or atelectasis in the lower right mid-lung field. The patient was entirely without symptoms

referable to his chest, but because of a family history of pulmonary carcinoma he was anxious to have further specialized investigation. At the time the patient was admitted to the hospital his father was dying from an inoperable carcinoma of the lung.

Roentgenograms of the chest made on admission revealed the area of infiltrate in the right lower mid-lung field which had been under observation between October and December, 1950. Particular attention was focused on what were thought to be three calcified lymph glands about the right tracheobronchial tree near the mediastnum (Fig. 5).

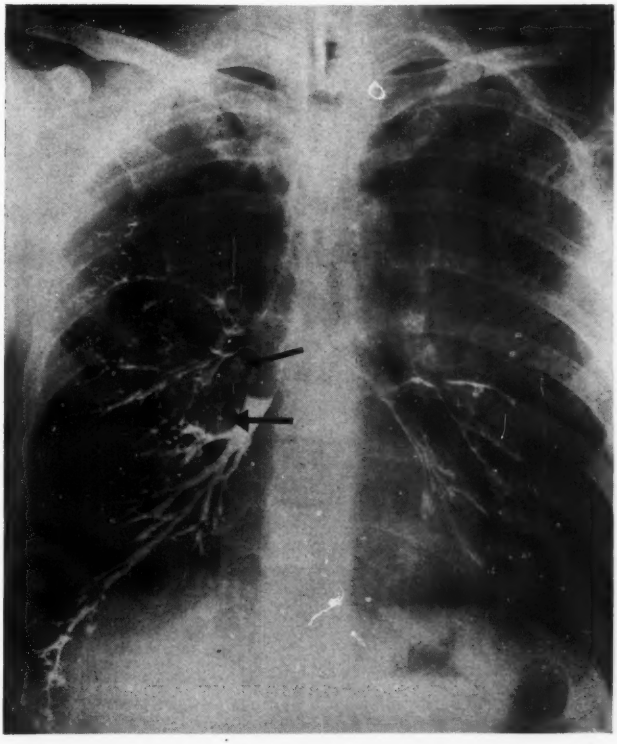


Fig. 6.—(Case 2.) Posteroanterior projection bronchogram showing relationship of calcified glands to lobar bronchi. Bronchiectasis not seen on this roentgenogram.

Bronchoscopic examination on Dec. 18, 1950, revealed entirely normal findings except for an area of pin-point erosion on the anterior wall of the right lower lobe bronchus. The orifice of the middle lobe bronchus was easily visualized and presented no evidence of obstruction or new growth. Material aspirated for cytologic study revealed atypical cells which were thought to arise from a primary malignant lung tumor. Acid-fast studies on the bronchial washings were negative for tubercle bacilli.

Bronchogram, performed following the bronchoscopic examination, revealed areas of saccular bronchiectasis involving one of the basal branch bronchi posteriorly in the right side. At the time of this examination the calcified lymph glands could be more accurately located above and below the right upper lobe bronchus and in the vicinity of the right middle lobe bronchus (Fig. 6).

A right posterior oblique projection roentgenogram again demonstrated the position of two calcified lymph glands above and below the right upper lobe bronchus, and the presence of a third calcified gland in the vicinity of the middle lobe bronchus. The middle lobe bronchus did not fill with oil despite the fact that the anterior divisions of the upper and lower lobe bronchi were well filled and adequately visualized. This excluded the possibility of improper positioning and failure of filling (Fig. 7). At the time of this examination the microscopic report on the bronchial washings was not available, and the significance of the calcified lymph glands was still not appreciated. It was our impression that we were dealing with a bronchiogenic carcinoma in the right middle lobe bronchus at a point distal to the orifice so that visualization by bronchoscopic examination was impossible. Exploratory thoracotomy was recommended.

Fig. 7.—(Case 2.) Right posterior oblique projection bronchogram. Note absence of filling of right middle lobe bronchus and presence of calcified body at point of origin of right middle lobe bronchus.

Operation was performed on Jan. 16, 1951. With the patient in the face-down position, the right thorax was entered through the bed of the sixth rib which was subperiosteally resected in its entirety. The right middle lobe was completely atelectatic and replaced by firm, dense, elastic tissue. There was an irregular area of increased consistency in the posterior portion of the right lower lobe where bronchiectasis had previously been demonstrated by bronchographic study. Palpation of the central portion of the hilum of the

lung revealed a large, very firm mass, approximately two to four cm. in diameter, which because of its location deep between the lobar vessels and bronchi was not accessible for direct biopsy. In view of the gross findings of atelectasis and obstruction of the middle lobe with bronchiectasis and areas of increased consolidation in the right lower lobe, as well as the findings of a mass in the vicinity of the hilum of the right lung, and previously described bronchial washings which revealed possible tumor cells, a right pneumonectomy was decided upon. Removal of the right lung was accomplished with a great deal of difficulty because of extensive scarring of the mediastinum. During the course of the dissection, two traction diverticula of the esophagus were encountered about the right main-stem bronchus. These diverticula, which were inseparably attached to the two calcified lymph glands along the main-stem bronchus, were amputated and the resultant defects in the esophagus closed with interrupted sutures of fine silk. Postoperatively, the patient did well and was discharged on his 12th postoperative day (Fig. 8).

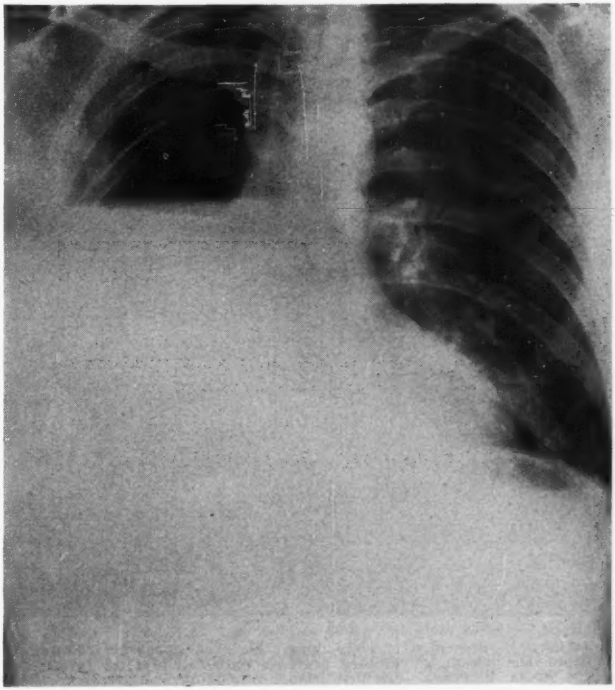


Fig. 8.—(Case 2.) Roentgenogram of chest following right pneumonectomy.

Dissection of the right lung in the pathology laboratory revealed no evidence of tumor. There was total atelectasis with far-advanced bronchiectasis and destruction of the entire middle lobe. This resulted from complete occlusion of the middle lobe bronchus by the contents of an extrabronchial lymph gland which had eroded through the wall of the bronchus and extruded into the lumen. A small pin-point erosion in the anterior wall of the basal branch bronchus with partial compression and bronchiectasis in the right lower lobe bronchus had also been produced by this same calcified extrabronchial gland. The firm mass which had been palpated at operation near the hilum of the lung corresponded in location to the extra-

bronchial calcified lymph gland just described. Following complete dissection of the middle lobe bronchus, one calcified body was seen to have eroded the inferior wall of this structure and then extruded into the lumen. Erosion at a second point in the opposite wall of the bronchus by pressure from the same calcified body had occurred so that it was lying in direct apposition with the pulmonary artery (Fig. 9).

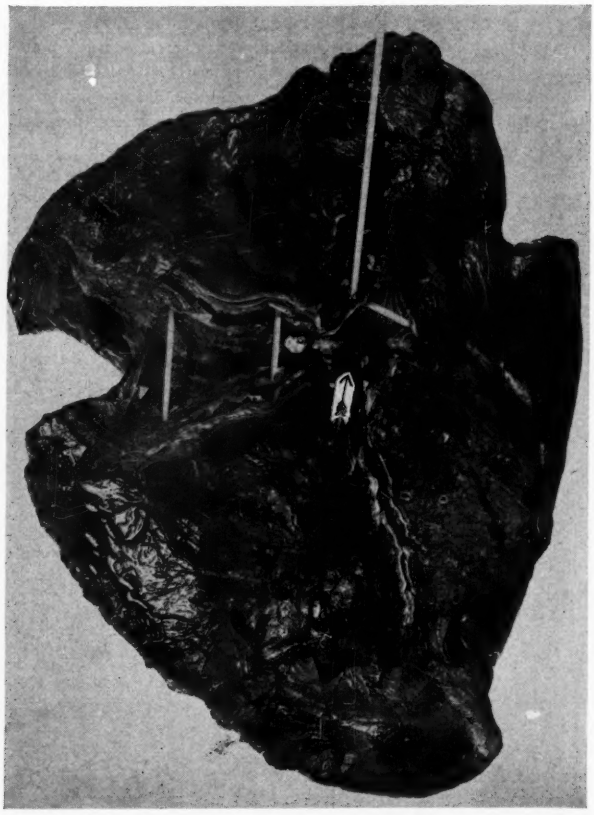


Fig. 9.—(Case 2.) Specimen of right lung. Note complete destruction of right middle lobe resulting from obstruction by calcified particles extruded into the lumen of the bronchus. Arrow points to extra bronchial calcified gland producing compression of posterior basal bronchus with bronchiectasis. Probe is in pulmonary artery.

COMMENT

The findings in Case 2 illustrate some of the difficulties encountered in differentiating preoperatively between bronchial compression due to calcified lymph glands or carcinoma. The issue was further clouded in this particular instance because of the finding of tumor cells in the bronchial washings. Obviously, this was a false positive report. Surgical removal of the right lung obviated future difficulties which could have resulted from erosion of the pulmo-

nary artery by the calcified body or the development of esophagobronchial fistulas if the traction diverticula of the esophagus had been permitted to go untreated.

CASE 3.—K. M., a 34-year-old white woman, was admitted to Good Samaritan Hospital on Sept. 17, 1947, with a diagnosis of tuberculoma, upper lobe, right lung. There was no history of cough, weight loss, or night sweats.

Posteroanterior projection roentgenogram of the chest, made on admission to the hospital, revealed three circumscribed, nodular, homogeneous densities, 4 cm. in diameter, in the upper lobe of the right lung (Fig. 10). At the time of this examination calcified bodies were described along the right lateral wall of the trachea, and several calcified lymph glands were

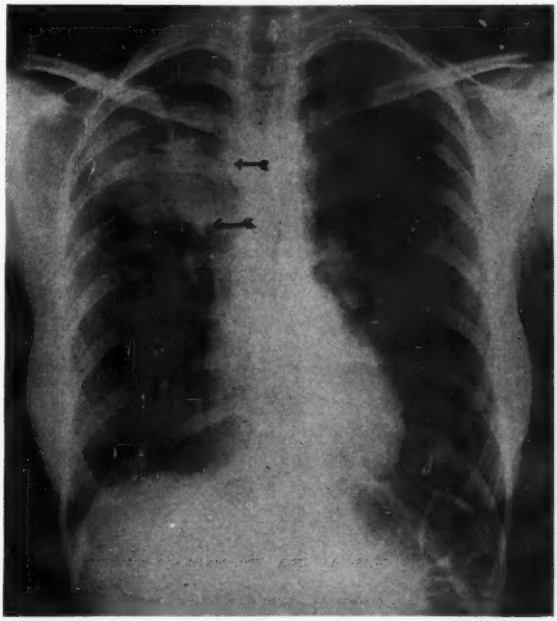


Fig. 10.—(Case 3.) Posteroanterior roentgenogram of chest showing tuberculoma of right upper lobe and calcified lymph glands along the trachea and right upper lobe bronchus.

noted in the vicinity of the right tracheobronchial tree just inferior to the tuberculoma. The serious significance of these findings, however, was not appreciated until the time of operation.

Bronchoscopic examination on Oct. 3, 1947, revealed almost complete occlusion of the right upper lobe orifice by what appeared to be compression from an extrabronchial mass. No actual tumor or ulcer was encountered. Bronchial washings were negative for acid-fast organisms and tumor cells.

Operation was performed on Oct. 17, 1947. The upper lobe of the right lung was almost completely replaced by firm elastic tissue, the central portion of which obviously contained fluid or pus. A right upper lobectomy which had previously been scheduled was found impossible because of the complete encirclement of the right upper lobe bronchus by firm calcified lymph glands which were deeply embedded in the wall of this structure. After a prolonged unsuccessful effort at dissection of these glands, pneumonectomy was

decided upon. Even this operation was found to be almost impossible to complete because of extensive calcification of the membranous wall of the main-stem bronchus and trachea with numerous calcified lymph glands inseparably embedded in the walls of these structures. One large accumulation of calcium presented in the mediastinum and was densely adherent to the pericardium. Dissection of the pulmonary vessels was made unusually difficult because of scarring in and about the mediastinum. After extensive dissection, an "S" shaped line of amputation across the right main-stem bronchus was finally developed and extended into the carina. This line of amputation passed between several calcified lymph glands, leaving just sufficient bronchial tissue so that good closure of the stump could be obtained with interrupted sutures of fine silk (Fig. 11). The calcified mediastinal plaque and a portion of the pericardium were removed with the right lung. Postoperatively, the patient did well and was discharged two weeks after operation.

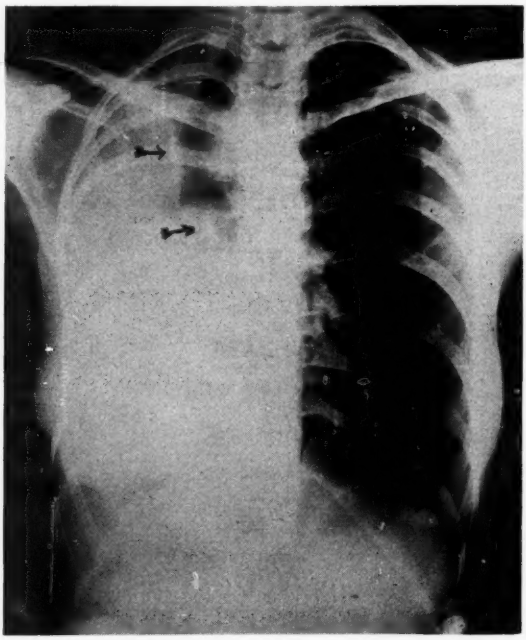


Fig. 11.—(Case 3.) Posteroanterior roentgenogram of chest following right pneumonectomy. Note calcified lymph glands along bronchial amputation stump and trachea.

Section of the lung showed the upper lobe to be occupied by several large intercommunicating thick-wall abscesses containing thick green viscid pus. Acid-fast organisms were demonstrated both on direct smear and culture of the pus contained in the abscesses.

COMMENT

The serious importance of the calcified lymph glands seen on the roentgenograms of the chest in Case 3 was not realized prior to operation. The mere anatomic presence of these glands made necessary a radical complete pneumonectomy instead of a simple right upper lobectomy in the management of a benign tuberculoma.

DISCUSSION

The serious significance of the presence of calcified lymph glands in and about the tracheobronchial tree probably has not received sufficient emphasis in the past. In patients with isolated areas of atelectasis due to bronchial compression by calcified lymph glands, the clinical history, physical findings, roentgenographic changes, and even endoscopic and bronchographic studies can be identical with the findings encountered in patients with atelectasis which is due to a peripherally located or extrabronchial pulmonary carcinoma.

The third case report illustrates the major surgical consideration an operator may be forced into by the incidental finding at the time of operation of deeply embedded calcified parabronchial lymph glands. The anatomic position of these calcified bodies about lobar bronchi may obviate adequate dissection and stump closure at this level and force the operator to amputate much higher with sacrifice of normal lung tissue.

Valuable information about the presence of unsuspected calcified lymph glands and their relationship to the tracheobronchial tree can be obtained preoperatively by more liberal use of heavy exposure roentgenograms and laminagrams of the chest in cases where the exact cause of the atelectasis or abnormal infiltrate is not immediately apparent.

CONCLUSIONS

1. The serious significance of calcified lymph glands is not always appreciated until open thoracic operations show these structures to be the real cause of lung pathology, the exact etiology of which was originally obscure.

2. The finding of calcified lymph glands by roentgenogram in and about the tracheobronchial tree is usually associated with dense scarring of the mediastinal and interlobar structures, and difficult surgical dissection at the time of operation can be anticipated.

3. The mere presence of nonobstructing calcified lymph glands about the lobar bronchi may necessitate the performance of more radical procedures than were preoperatively anticipated to remove lesions for which more conservative surgery is ordinarily recommended.

4. Extrabronchial compression, with or without erosion by calcified lymph glands, can produce all of the symptoms and roentgenologic findings of primary pulmonary carcinoma.

5. As with other nonmalignant lesions producing bronchial obstruction, complete excision of the destroyed portions of lung with the calcified lymph gland will invariably result in a cure.

6. More careful preoperative roentgenologic studies of the chest using Potter-Bucky techniques and laminagrams are invaluable in demonstrating the presence of calcified lymph glands and their relationship to portions of the tracheobronchial tree which might be obstructed by compression.

REFERENCES

1. Lamy, M., Jammet, M. L., Lamotte, M., and Wolfromm, H.: Pulmonary Atelectasis and Emphysema in Course of Tuberculosis of Tracheobronchial Glands in Children, Rev. tuberc. 6: 301-305, 1941.

2. Barsby, B.: Tuberculous Obstructive Emphysema in Children, Lancet **1:** 627-630, 1941.
3. Hughes, J. G., and Simpson, W. L.: Bronchiectasis Following Atelectasis in Tuberculosis of Infancy; Role Played by Enlarged Glands and Granulation Tissue, J. Pediat. **17:** 197-209, 1940.
4. Pray, L. G.: Obstructive Emphysema in Infancy Due to Mediastinal Glands; Case, J. Pediat. **25:** 253-256, 1944.
5. Coleman, F. P., and Bunch, G. H., Jr.: Acquired Non-malignant Esophagotracheobronchial Fistula, J. THORACIC SURG. **19:** 542-558, 1950.
6. Head, J. R., and Moen, C. W.: Late Non-tuberculous Complications of Calcified Hilus Lymph Nodes, Am. Rev. Tuberc. **60:** 1-14, 1949.
7. Buckles, M. G.: The Surgical Aspects of Calcified Hilar Lymph Nodes, Ann. Surg. **132:** 972-979, 1950.